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REVIEW

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 β-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	*Candida albicans* germ tube
CI	Colonization index
DLY	Discounted life year
FIO_2	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_2	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_2	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.

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.

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 predetermined 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 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.

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

Risk factors
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

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 → 3)-β-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 ß-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.

Conflict of interest Benoit Guery was consultant for GSK, Wyeth, and Pfizer. Maiken C Arendrup received honoraries as a speaker 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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REVIEW

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Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment

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Abstract *Background:* Invasive candidiasis and candidemia are frequently encountered in the nosocomial setting particularly in the intensive care unit (ICU). *Objective 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 an European expert panel discussion. *Results and conclusions:* Empiric and directed treatment for invasive candidiasis are predicated on the hemodynamic status of the patient. Unstable patients may benefit from broad-spectrum antifungal agents, which can be narrowed once the patient has stabilized and the identity of the infecting species is established. In stable patients, a more classical approach using fluconazole may be satisfactory provided that the patient is not colonized

with fluconazole resistant strains or there has been recent past exposure to an azole (<30 days). In contrast, pre-emptive therapy is based on the presence of surrogate markers.

Keywords Antifungal · Azole · *Candida* · Candidiasis · Echinocandins · Invasive candidiasis · Intensive care · Polyenes

Abbreviations

aPTT	Activated partial thromboplastin time
CAGT	*Candida albicans* germ tube
CI	Colonization index
DLY	Discounted life year
FIO_2	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_2	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_2	Mixed venous oxygen saturation
WBC	White blood cell

Introduction

The treatment of invasive candidiasis and candidemia can be schematically described as prophylactic, pre-emptive, empiric or curative. Prophylactic treatment covers all the situations where the patient is not infected and lacks the signs and symptoms of infection. In pre-emptive treatment, based on evaluation of the patient's risk factors combined with positive surrogate markers of infection, the patient is deemed to be at significant risk of being infected and this increased risk justifies a treatment; the goal is to decrease *Candida*-related mortality. Empiric therapy describes individuals with symptoms of infection with no obvious source who merit therapy based on clinical grounds. In many studies the lines between the latter two groups of treatment are not always very clear. Finally, curative treatment focuses on a microbiologically documented pathogen.

The need for appropriate and early treatment

Appropriate therapy is a major factor associated with a good prognosis in fungal infection. In a 5-year study, 207 patients were diagnosed with invasive candidiasis and candidemia of which 52% were due to *Candida albicans* [1], 64 (32%) were given empirical therapy, of which 51 (26%) was deemed adequate. Adequate empirical therapy was independently associated with a reduced risk of death (crude mortality rate 27 vs. 46%; OR 0.46). A study performed in 28 hospitals in Spain showed that early therapy (treatment started within the 48 h after the onset of candidemia) was associated with a higher probability of survival [2]. In another study, Garey et al. [3] also emphasized the importance of the timing of treatment. In this study, mortality rates were lower for patients who began therapy on day 0 (15%) compared to day 1 (24%), day 2 (37%) or later (41%). The delay was defined as the difference between blood drawing and treatment onset. A comparable result was found by Morrell et al. [4]: in this study, the authors showed that administration of antifungal treatment 12 h after having the first positive blood sample for culture was an independent marker of hospital mortality. In non-neutropenic critically ill patients with sepsis, inappropriate empirical antimicrobial therapy was frequently associated with presence of invasive fungal infection and contributed to an increased mortality rate [5]. Kumar et al. also demonstrated increased mortality rates in patients with fungal sepsis and shock associated with delays in the initiation of therapy: every hour delay was associated with a 12% decreased probability of survival [1, 6].

Prophylactic antifungal treatment in the ICU

Candida spp live as commensals in the gut lumen and on cutaneous surfaces. As has been previously discussed, there is a strong link between *Candida* colonization and invasive candidiasis; therefore it would seem clinically relevant to decrease the fungal load with an antifungal drug. Since morbidity and mortality rates in patients with invasive candidiasis infections are high, the use of prophylaxis seems very attractive. This prophylactic strategy has been validated in different subsets of patients such as neutropenic patients with hematological malignancies, or after bone marrow transplant [7]. In the ICU, this approach remains under discussion. There is a need to better identify the ICU patient profile that could benefit from prophylactic antifungal therapy as the following studies illustrates.

In a medical/SICU, Garbino et al. [8] compared two groups of patients with selective digestive decontamination (SDD) with or without fluconazole (100 mg daily).

Their results showed that 90% of candidemia episodes occurred in the placebo group, but the crude mortality rate remained unchanged. In selected high-risk surgical patients undergoing relaparotomy for bowel perforation or suture leakage, Eggimann et al. [9] used intravenous fluconazole prophylaxis and showed prevention of both colonization and invasive intra-abdominal invasive candidiasis. An important observation in this study, compared to the previously described Garbino trial, is the dose of fluconazole used (400 mg daily), which was a curative rather than a prophylactic dose. Moreover, it is difficult to know, from the type of patients recruited, whether it was genuine prophylactic treatment as the study mostly involved a high-risk surgical population. Hence applying current criteria the study may be better described as evaluating pre-emptive or empirical treatment. This approach is further supported by data from Pelz et al. [10] who showed in a prospective study of 159 ICU patients that fungal burden was strongly associated with infection. In this trial, having two or more sites positive in a single day was associated with an odd ratio of 8.2. Recently, Manzoni et al. [11] showed a significant decrease of invasive candidiasis with fluconazole prophylaxis, although this was in neonates; no effect on mortality was observed.

A systematic review of published antifungal prophylaxis studies carried out in the ICU setting evaluated whether systematic antifungal therapy could decrease morbidity and mortality [12]. Prophylaxis with an azole was associated with a reduced rate of candidemia, as well as a decrease of *Candida*-attributable mortality and overall mortality rates. While the systematic review was based on highly divergent studies, addressing different methodologies, different patient populations and using different antifungal therapy, the conclusions of this review nevertheless lend some support to the hypothesis that prophylaxis could be of benefit in selected subsets of patients. The results of five meta-analyses on this subject are nicely summarized in a review paper by Pfaller et al. [13] and support a policy of prophylaxis in selected patients, with a reduction of the risk of invasive form by 50 to 80%. The effect was however, less clear on mortality or on the emergence of azole-resistant *Candida* species. The selection of patient groups who will benefit from prophylaxis is still unclear, and there is a need for additional data.

Prophylactic therapy should also be scrutinized in relation to potential deleterious consequences such as selection of resistant strains and drug-related toxicity [14]. Several studies have suggested a potential link between prophylactic use of fluconazole and an increase in resistance or selection of azole-resistant species. Bassetti et al. [15] observed this phenomenon during a 5-year study from Brazil. Interestingly, although not strictly confined to ICU patients, a retrospective study attempted to describe all cases of nosocomial candidemia that occurred in patients receiving at least 3 days of systemic antifungal drugs [16]. Non-albicans species, mainly *C. parapsilosis*, and *C. tropicalis*, the two most prevalent non-albicans *Candida* species in this country, caused 75% of these infections. Of the 20 patients studied, 40% had cancer, and when compared to controls, risk factors were mucositis, longer stay in the ICU, longer periods of hyperalimentation, mechanical ventilation, urinary catheter, and use of broad-spectrum antibiotics. Similarly, one case report documented a *C. glabrata* isolate with a specific profile of resistance in a critically ill patient, that was resistant to both amphotericin B and caspofungin [17]. In a retrospective analysis of two ICU patient cohorts, Rocco et al. [18] analyzed the effect of fluconazole administration on *Candida* sensitivity. As use of this antifungal agent increased, an increase in *Candida* spp that were resistant to fluconazole was observed.

Empiric and pre-emptive treatments

Several drugs have been tested in these settings and could therefore be proposed for treatment. A retrospective audit of 225 SICU patients receiving antifungal therapy showed that fluconazole was the most frequently prescribed antifungal drug (1,846 patient-days), followed by amphotericin B (251 patient-days) [19]. These data are not representative of current usage patterns as the study was carried out between 2001 and 2002. The drugs were prescribed empirically (44%), for pre-emptive therapy in colonized patients (43%) or in those with candidiasis (12%). The authors concluded that efforts to identify patients who warrant pre-emptive antifungal therapy for invasive candidiasis could dramatically change antifungal prescribing patterns in this setting. However, there are no substantiating data from randomized trials to support the empiric or pre-emptive use of antifungal agents in the ICU setting.

Piarroux et al. [20] tried to assess the efficacy of pre-emptive antifungal therapy in preventing proven candidiasis in critically ill surgical patients. In a total of 933 patients, they evaluated, as a primary endpoint, the frequency of proven candidiasis within a prospective period during which patients with a corrected colonization index ≥ 0.4 received early pre-emptive antifungal therapy with fluconazole. *Candida* infections occurred more frequently in the control cohort (7 vs. 3.8%; $P = 0.03$). The incidence of SICU-acquired proven candidiasis significantly decreased from 2.2 to 0%. The authors concluded that a targeted pre-emptive strategy may be effective in preventing acquisition of proven candidiasis in SICU patients.

Treatment of documented infection

In recent guidelines the drugs proposed as first-line therapy have usually been selected based on the clinical status of the patient [14, 21]. The reason for such risk-based strategy is the assumption that critically-ill patients may benefit most from a highly-active therapy, and that there is no room for failure. If narrow-spectrum antifungals are chosen they may not cover the pathogen involved. This hypothesis may be supported by the recent studies suggesting that early institution of adequate antifungal therapy may significantly reduce mortality in patients with candidemia, as described above [3, 4, 6]. Thus although this is not evidenced based medicine, retrospective data point to a differentiation between hemodynamically stable from hemodynamically unstable patients. It can be assumed that a clear line can be drawn for patients in septic shock, an intermediate risk group should be proposed for patients with severe sepsis. It seems appropriate therefore, to first describe the specific definitions before discussing the treatment itself.

Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock

After its initial definition in 1991, the diagnosis of sepsis was revisited in 2003 and the list of clinical signs and symptoms was expanded, reflecting bedside experience [22]. The definition of a hemodynamically unstable patient with sepsis needs to be applied according to this classification. Four stages are differentiated: systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis (with organ dysfunction), and septic shock.

Sepsis is defined by the presence of both infection and SIRS. The diagnostic criteria for sepsis are summarized in the Electronic supplement material. Severe sepsis refers to sepsis complicated by organ dysfunction, and septic shock represents a state of acute circulatory failure characterized by persistent arterial hypotension despite adequate volume resuscitation in the absence of other causes of hypotension.

A patient with septic shock is clearly characterized as a hemodynamically unstable patient; SIRS and sepsis patients however, do not fit this definition. Most of the debate or controversy regarding the identification of hemodynamically unstable patients focuses on the patient with severe sepsis, i.e. a patient with organ failure. They are at higher risk of progressing to septic shock if treatment is inadequate. Although they do not completely fit the definition of 'hemodynamically unstable', it may be prudent to classify these patients as high-risk and therefore propose a line of treatment identical to that for the well-defined unstable group using additional markers like plasma lactate.

The available drugs and their main treatment outcomes in the ICU

Treatment of invasive candidiasis and candidemia has changed significantly in recent years due to a growing number of newly available agents, and the resulting modification of guidelines. Case series, published in the 1990s, used mainly fluconazole and amphotericin B and showed no difference between the two groups [2]. The main concern with amphotericin B was its toxicity.

Currently available drugs to treat invasive candidiasis and candidemia include amphotericin B and its derived lipid formulations, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin. The focus of this review will be on data from the most recently introduced agents—caspofungin, anidulafungin and voriconazole. Most *Candida* spp are usually susceptible to these agents, but resistance has been described either naturally or after previous exposure to the drugs. For example, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. lusitaniae* can present resistance to the primary agent or require a dosage increase (Table 1).

Echinocandins are the most recently introduced class of antifungal drugs. This new class includes caspofungin, anidulafungin, both now available in Europe, and micafungin, which is not yet marketed. Echinocandins are fungicidal drugs that are active against both *C. albicans*

Table 1 Minimum inhibitory concentration (50/90%) of antifungal agents against the most common *Candida* species

	Amphotericin B (μg/ml) [44]		Flucytosine (μg/ml) [44]		Fluconazole (μg/ml) [44]		Voriconazole (μg/ml) [44]		Caspofungin (μg/ml) [44]		Anidulafungin (μg/ml) [44]	
	MIC_{50}[c]	MIC^{c}_{90}	MIC^{c}_{50}	MIC^{c}_{90}	MIC^{c}_{50}	MIC^{c}_{90}	MIC^{c}_{50}	MIC^{c}_{90}	MIC^{c}_{50}	MIC^{c}_{90}	MIC^{c}_{50}	MIC^{c}_{90}
C. albicans	0.06	0.25	0.13	1	0.25	2	0.03	0.06	0.5	0.5	0.03	0.03
C. glabrata	0.13	0.5	0.13	0.13	8	32	0.25	1	0.5	1	0.03	0.13
C. parapsilosis	0.1	0.5	0.13	0.13	1	2	0.03	0.06	2	2	2	2
C. tropicalis	0.13	0.5	0.13	0.5	0.5	16	0.06	2	0.5	1	0.03	0.13
C. krusei	0.25	0.5	4	32	32	>64	0.5	1	1	2	0.06	0.13
C lusitaniae	0.13	0.5	0.13	0.13	0.5	2	0.03	0.06	1	2	0.06	0.25

and non-albicans species. Caspofungin has been shown to be as effective as, and better tolerated than, conventional amphotericin B in patients with invasive candidiasis [23]. This improvement in tolerance could be important in the management of the ICU patient, particularly in those with renal failure. Evaluation of this drug in ICU patients has been carried out in a post hoc analysis of the Mora-Duarte trial [23] specifically in relation to risk factors and outcome. The authors found that even after accounting for differences in the Apache II score, patients starting the study drug in the ICU were more likely to die than those starting it outside the ICU [24]. The all-cause mortality among candidemic ICU patients was 45%. There was no statistically significant difference in all-cause or *Candida*-attributable mortality rate between patients treated with either caspofungin or amphotericin B, but the incidence of drug-related adverse events and of nephrotoxicity was significantly lower in the caspofungin group. These findings suggest that caspofungin could be an attractive choice in ICU patients in whom renal failure or prior azole exposure limit the use of other antifungal agents. It must however be underlined that, beside toxicity, the efficacy between the two drugs showed no significant differences. Pappas et al. [25] compared two dosages of micafungin to caspofungin. The results showed that 100 mg daily and 150 mg daily were non-inferior to a standard dosage of caspofungin for the treatment of candidemia. The authors did not find any statistical difference in mortality, relapsing and emergent infection or adverse events between the drugs. Of note, whereas micafungin has been licensed, its approved use in Europe is restricted to cases where other antifungals are not appropriate, in view of its potential risk for the development of liver tumors. Table 2 summarizes the main results of the studies involving echinocandins.

It has been shown, mostly through study of antibiotics, that the pharmacokinetic/pharmacodynamic profile of ICU patients is different from that of non-ICU controls, with large variations in the volume of distribution and renal clearance. Nguyen et al. [26] analyzed the factors influencing caspofungin concentrations in ICU patients; they showed that body weight <75 kg and albumin concentration >23.6 g/l was associated with higher levels of caspofungin than predicted.

Anidulafungin has recently been studied in a randomized double blind trial of treatment for invasive candidiasis [21]. In this study, anidulafungin was compared with fluconazole, with the primary efficacy analysis assessing the global response at the end of intravenous therapy. At this endpoint, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole ($P = 0.009$). In this population, 21% in the anidulafungin group and 17% in the fluconazole group had an Apache II score >20. Overall, the authors concluded that anidulafungin was not inferior to and suggested to be more efficacious than fluconazole for the primary treatment of candidemia, with a safety profile similar to that of fluconazole. The authors also commented that the success rate at the end of intravenous anidulafungin in this trial was similar to that reported in a study evaluating caspofungin in the primary treatment of invasive candidiasis [23].

There are also new azoles that should be considered for therapy of invasive candidiasis in ICU patients. Voriconazole is recommended as first-line of therapy in invasive aspergillosis, but several studies suggest a potential role in candidiasis. Ostrosky-Zeichner et al. [27] showed that voriconazole was efficient as a salvage therapy in this indication. In a randomized study in non-neutropenic patients with candidemia, voriconazole was compared to a regimen of amphotericin B followed by fluconazole [28]. Half of the patients in each group were in the ICU. The results showed that voriconazole was as effective as the control regimen in the treatment of candidemia, with significantly fewer side-effects. In this study, amphotericin B was only administered for a median of 4 days, underlining that even short courses of this drug could be associated with significant adverse effects. One limitation regarding extrapolation of voriconazole use for ICU patients is that the i.v. formulation of

Table 2 Main studies in non neutropenic patients evaluating echinocandins in invasive candidemia

Author (references)	Year	Antifungal agents	No of patients	Success[a] (mITT) %	Success for Apache II > 20 *n* (%)	Crude mortality (%)	AE (%)
Mora-Duarte [23]	2002	Amphotericin B	125	61.7	10/23 (43.5)	30.4	75.2
		Caspofungin	114	73.4	12/21 (47.1)	34.2	42.1
Reboli [21]	2007	Anidulafungin	127	75.6	No difference between the groups	22.8	24.4
		Fluconazole	118	60.2		31.4	26.4
Kuse	2007	Micafungin	247	74.1	31/39 (79.5)	18	43.2
		LFAB	247	69.6	33/37 (89.2)	17	50.9
Pappas [25]	2007	Micafungin 100	191	76.4	21/35 (60)	29	22
		Micafungin 150	199	71.4	22/40 (55)	33.2	22.8
		Caspofungin	188	72.3	21/36 (58.3)	26.4	23.8

mITT Modified intention to treat, *EOT* end of treatment, *AE* adverse event, *LFAB* lipid formulations of amphotericin B

[a] Success evaluated at the end of IV therapy

voriconazole is contra-indicated in patients with a creatinine clearance of <50 ml/min.

Antifungal therapy based on patient's clinical status

A treatment algorithm for invasive candidiasis was recently proposed by Spellberg et al. [29]. They proposed the hemodynamic status of the patient as the main criterion for selection of pharmacological intervention (Fig. 1).

In hemodynamically stable patients without organ dysfunction, fluconazole is a reasonable choice for empiric therapy or microbiologically documented infection, based on its highly favorable safety profile and low costs [30]. Alternative drugs to be considered are echinocandins (caspofungin or anidulafungin), voriconazole, or amphotericin B (deoxycholate or liposomal). The duration of treatment should be continued for 2 weeks after the last positive culture.

However, if the likelihood of azole-resistant species is high, based on local resistance reports, if the patient is colonized with azole-resistant species, or recently exposed to an azole (within 30 days) as prophylactic treatment, fluconazole should be avoided and the use of echinocandins or polyenes is preferred.

In contrast, patients who are hemodynamically unstable with septic shock or who have signs of severe sepsis require potent therapy, with a broad-spectrum agent that has a minimum toxicity. To achieve this aim, echinocandins are a preferred first choice (caspofungin or anidulafungin), as has been supported by the results of the Reboli study [21]. Alternatively, lipid formulations of amphotericin B (LFAB) may be used in unstable patients. Conventional amphotericin B is associated with a high risk of side effects e.g. renal failures and can therefore not be recommended in critically ill patients. Transition from an echinocandin or LFAB to fluconazole or voriconazole is recommended once patients are clinically stabilized and the isolate has been confirmed to be azole-susceptible.

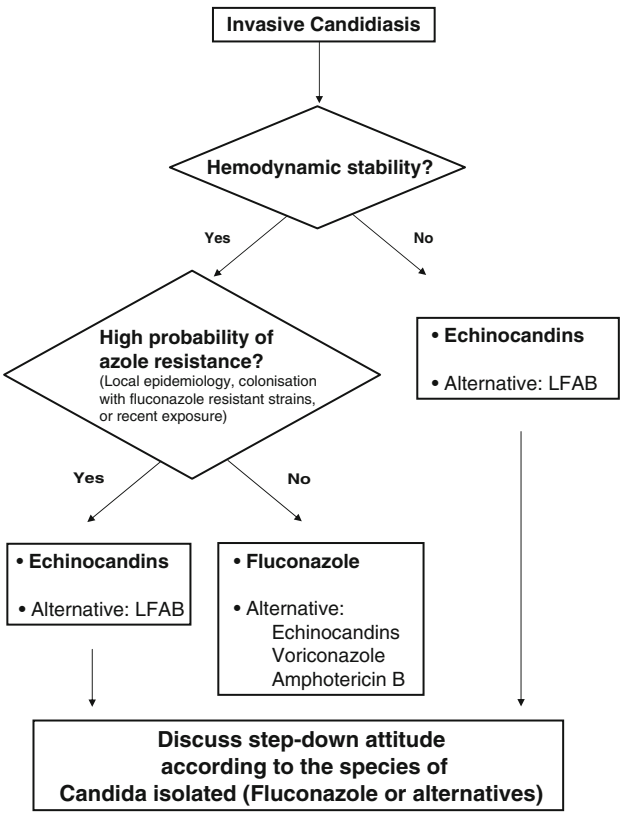

Fig. 1 Algorithm summarizing the practical treatment of documented candidiasis in the ICU. *LFAB* Liposomal form of amphotericin B

Combination therapy

The poor prognosis attributed to *Candida* sepsis in the ICU has provoked much debate on the potential beneficial effect of combination therapy, but currently few studies have been conducted in this area. In a study comparing fluconazole with amphotericin B versus fluconazole alone, the combination resulted in a better response rate in the combination group, although associated with significant amphotericin B toxicity [31]. Flucytosine is another classical agent used in combined therapy; because of its ability to penetrate the blood brain barrier, this drug is often added to amphotericin in cerebral, ocular and meningeal localizations [32, 33]. Over many years different studies have described multiple antifungal combinations for the treatment of invasive fungal infections. The scientific rationale to support the use of combination therapy is based on the hypothesis that the infecting pathogen is more effectively treated if drugs with different mechanisms of action are combined. Recently, one study on *Aspergillus* infection in transplant patients obtained better results with voriconazole plus caspofungin compared with lipid formulation of amphotericin B [34]. To date, the use of combination antifungal therapy in patients with invasive candidiasis is not recommended and further studies are required.

Cost-effectiveness of these approaches

In a cost-effectiveness analysis concerning ICU patients, Golan et al. [35] showed that in suspected infections that have not responded to antibiotic treatment, empirical fluconazole could reduce mortality at an acceptable cost. They also concluded that empirical strategies are not justified in low-risk patients. Recent work by Chen et al. [36] further developed this approach by using a high dose

of fluconazole in ICU patients suspected to have invasive candidiasis. The rationale for this approach was the observed increasing percentage of non-albicans *Candida* with a decreased susceptibility to fluconazole. In this study, high-dose fluconazole was the more effective but also more expensive treatment strategy compared to low-dose therapy, with a cost-effectiveness rate of $55,526 per discounted life year (DLY) saved. The authors concluded that this strategy should reduce mortality at an acceptable cost. However, it should be noted that these models have not taken into account the results of the recent study suggesting a significantly better outcome with anidulafungin compared with fluconazole [21] which would justify a formal cost-effectiveness analysis comparing anidulafungin with fluconazole-based strategies.

Catheter management in the ICU patient

It has been known for a long time that intravascular catheters are significant risk factors for the development of candidemia [37, 38]. The initial retrospective study by Rex et al. [39] suggested the need to remove all intravascular catheters in candidemia. In the subset of patients who had a catheter in place at the time of their first positive blood culture, removal and replacement of all lines was associated with a reduction in the mean duration of candidemia. In a study performed in cancer patients, central venous catheter removal was only effective in improving the response to antifungal agents when the candidemia could be related to the catheter [40]. In ICU patients, however, it seems reasonable to propose catheter exchange in all patients with candidemia whenever logistically feasible.

Pharmacokinetics profile

The pharmacokinetics properties of an antimicrobial agent are essential to promote microbiological eradication and clinical efficacy. ICU patients with invasive *Candida* infections present special characteristics: higher disease severity, organ dysfunction (particularly in case of cardiovascular, renal and hepatic failure), co-morbidities and drugs. In these patients, not only plasma concentrations but also tissue penetration of the antifungal drug is crucial to obtain favorable clinical and microbiological results. The pharmacokinetic analyses of echinocandins suggest that these drugs behave like concentration-dependent molecules, thus high intermittent dosing may be desirable for the treatment of invasive candidiasis. The potential limitations of high drug doses include a paradoxical decrease in microbial kill (the eagle effect) as well as the toxicity of high intermittent doses [41]. Finally the main difference between caspofungin, micafungin, and anidulafungin relates on the elimination profile, the half life and the distribution volume [42]. Additional pharmacokinetics studies are needed in ICU patients [43].

Conclusion

The choice of empiric therapy or therapy for documented infection is dependent on the hemodynamic status of the patient, and will probably involve the use of drugs from the echinocandin family if the patient is unstable. On the other hand, a stable patient can be treated with azole as long as known colonization with a fluconazole-resistant strain, local epidemiology or previous exposure to this drug does not demand a broader antifungal spectrum. Current guidelines have to be re-evaluated as the availability of new molecules, new tests and new diagnostic procedures, raise important questions that have to be answered, specifically in this subset of patients.

Expert opinion

Intensive care unit patients represent a diverse population for the treatment of invasive candidiasis; the clinical presentation and vital prognosis are usually the key issues of the treatment. According to the current literature, the use of prophylactic therapy in high-risk individuals such as surgical ICU patients warrants consideration. In documented *Candida* infection and those patients highly suspected of having invasive candidiasis, the choice of therapy depends on the hemodynamic status of the patient and previous azole exposure or resistance. In the hemodynamically unstable patient, a broad spectrum fungicidal drug like an echinocandin is the preferred choice. Since the diagnosis of invasive candidiasis occurs in the late phase of the evolution of the disease (either a positive blood culture, or a high colonization index for example), the main challenge for the future is to elaborate diagnostic methods that will give us the opportunity to identify the patients affected by these infections earlier in the course of the disease. Moreover, beyond diagnosis correct identification of the pathogen and its associated resistance pattern needs to be improved. Finally, in ICU patients, combination antifungal therapy remains to be explored.

Conflict of interest Benoit Guery was consultant for GSK, Wyeth, and Pfizer. Maiken C. Arendrup received honoraries as a speaker 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, invited). 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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