CLINICAL MICROBIOLOGY AND INFECTION

VOLUME 17, SUPPLEMENT 5, SEPTEMBER 2011

European Expert Opinion on the Management of Invasive Candidiasis in Adults

GUEST EDITOR

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Publication of this supplement was funded by Pfizer International Operations.

ORIGINAL ARTICLE 10.1111/j.1469-0691.2011.03615.x

European expert opinion on the management of invasive candidiasis in adults

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Abstract

This report discusses the present status of antifungal therapy and treatment options for candidaemia, considered by experts in the field in Europe. A conference of 26 experts from 13 European countries was held to discuss strategies for the treatment and prevention of invasive candidiasis, with the aim of providing a review on optimal management strategies. Published and unpublished comparative trials on antifungal therapy were analysed and discussed. Commonly asked questions about the management of candidaemia were selected, and possible responses to these questions were discussed. Panellists were then asked to respond to each question by using a touchpad answering system. After the initial conference, the viewpoint document has been reviewed and edited to include new insights and developments since the initial meeting. For many situations, consensus on treatment could not be reached, and the responses indicate that treatment is likely to be modified on a patient-to-patient basis, depending on factors such as degree of illness, prior exposure to azole antifungals, and the presence of potentially antifungal drug-resistant *Candida* species.

Keywords: candida, candidaemia, consensus, guidelines, therapy
Original Submission: 28 January 2011; **Revised Submission:** 1 June 2011; **Accepted:** 8 June 2011
Editor: D. Raoult
Clin Microbiol Infect 2011; **17** (Suppl. 5): 1–12

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Introduction

Invasive candidiasis, mostly candidaemia, is associated with a high global mortality rate, ranging from 36% to 63% in different patient groups [1–4], and represents a significant burden on the public health system in terms of patient management and healthcare costs. In a prospective hospital-based population study in seven European countries, rates of candidaemia ranging from 0.20 to 0.38 per 1000 hospital admissions were reported [3]. Approximately half of all *Candida* infections now occur in intensive-care units (ICUs) [5,6]. An increase in the incidence of candidaemia between 1999 and 2006 was reported from several countries [7–9].

Although *Candida albicans* is still the leading cause of invasive candidiasis in most clinical settings [3,8], there has been a significant pathogen shift towards other *Candida* species over the past few years in some patient groups [3,7,10]. The

changing epidemiology has been partly attributed to selection of less sensitive *Candida* strains, owing to the widespread use of fluconazole as a prophylactic and therapeutic agent [11,12].

Over the years, a variety of new antifungal drugs have been introduced. Although these developments mean that clinicians now have more choices when selecting an antifungal drug, the most effective treatment regimens for invasive candidiasis are uncertain. In 1997, Edwards *et al.* [13] published the results of an international conference to develop a consensus on the management of severe *Candida* infections. In an attempt to review the treatment strategies for invasive candidiasis with a global European perspective, we held a similar meeting to that of Edwards *et al.* [13], based on the views and current practices of a panel of European experts in clinical mycology. As in the previous study, where opinions differed between the experts, the aim was to present the full diversity of opinion from all participants.

Participants and Consensus Methods

The panel consisted of 26 experts (infectious diseases physicians, medical microbiologists, mycologists, haematologists, and intensivists) from 13 European countries. Each was invited because of their expertise in studies on candidiasis and the management of patients with *Candida* infections.

A list of questions regarding treatment strategies for severe *Candida* infections in adults was developed by two of us (B.J.K. and P.E.V.). As in the previous consensus meeting [13], questions were reviewed and edited during the meeting, and the wording of possible answers to the questions was reviewed, extensively discussed, and revised. Subsequently, the issues were discussed and the answers to the questions were voted on anonymously, by the use of electronic keypad devices. The moderators of the meeting (B.J.K. and P.E.V.) did not vote. The manuscript generated from the meeting results was distributed, reviewed, edited, and discussed by all participants to include new insights and developments since the initial consensus meeting. This report discusses the full spectrum of responses to each question and treatment preferences.

Results

Initial management of candidaemia

Should all patients with a positive blood culture for Candida be treated?

Background: Nosocomial candidaemia is associated with high levels of mortality in critically ill patients [2], especially if antifungal therapy is delayed [14,15]. However, up to 85% of patients with candidaemia do not receive appropriate antifungal therapy for 24 h or more until blood culture results are known [14]. Whereas transient, self-limited candidaemia may resolve without antifungal therapy, patients with candidaemia who will recover without antifungal therapy are currently impossible to identify.

Responses: All panellists indicated that they would treat all patients with a *Candida*-positive blood culture, irrespective of clinical status and underlying risk factors. Reluctance to do so among some clinicians is likely to be attributable to confusion about the significance of positive blood cultures from samples taken via a central intravascular catheter. In a retrospective review of 155 episodes of vascular catheter-related candidaemia in cancer patients, the frequency of autopsy-proven candidiasis was similar irrespective of whether blood was obtained via a central catheter or from a peripheral site [16]. A recent series of 370 episodes of candidaemia reported by Kullberg *et al.* [17] suggested that positive blood cultures for *Candida* from samples obtained via an indwelling intravascular line should never be disregarded in a symptomatic patient with concomitant signs of infection. These studies demonstrate the need to treat all patients with positive blood cultures irrespective of the site of blood collection.

What determines the choice of initial antifungal therapy in a patient with candidaemia before the species has been determined?

Background: It is difficult to know which antifungal drug is the most effective to use before the yeast species and susceptibility have been determined. The severity of illness (ICU admission or haemodynamic instability) is felt by most to be a major determinant in selecting an appropriate antifungal agent, in addition to the local epidemiology of *Candida*. A recent French multicentre ICU cohort study reported that 17% of *Candida* isolates were less susceptible to fluconazole [18]. However, no clinical factor to guide the choice of therapy was apparent [19]. We assumed previous exposure to azoles (either as prophylaxis or as treatment) to be a major risk factor for colonization with less susceptible *Candida* species, and thus considered 'azole-naïve' patients to be separate from azole-exposed patients when selecting initial therapy.

Sample case. An adult recently admitted to the ward with uncomplicated sepsis, is azole-naïve, has normal liver and renal function, and has candidaemia. What would be the initial choice of therapy?

Background: In most European countries, six antifungal drugs have been approved for candidaemia: fluconazole, amphotericin B desoxycholate (d-AmB), voriconazole,

anidulafungin, caspofungin, and micafungin. Recent clinical trials have demonstrated non-inferiority or superiority of the newer antifungal agents as compared with conventional d-AmB or fluconazole. Caspofungin was shown to be non-inferior to d-AmB in patients with invasive candidiasis (response rates of 73% vs. 62% at end of intravenous study drug administration (end of treatment (EOT)), p 0.09) [20,21], whereas voriconazole was non-inferior to a regimen of d-AmB followed after 3–7 days by fluconazole in patients with candidaemia (response rates of 70% vs. 74% at EOT, p 0.42) [5]. Both caspofungin and voriconazole were better tolerated than d-AmB, and were associated with fewer drug-related side effects. Three further phase III clinical trials showed that anidulafungin and micafungin are also effective antifungal drugs for the treatment of invasive candidiasis [22–24]. Anidulafungin was superior to fluconazole in 261 patients with candidaemia or invasive candidiasis, with global response rates of 75.6% vs. 60.2% at EOT (p 0.01) [22], and superior efficacy in infections caused by *C. albicans* (81.1% vs. 62.3%) and non-*albicans* species (71.1% vs. 60.0%), with the exception of *Candida parapsilosis* [22]. Intravenous micafungin (100 mg daily) was non-inferior to liposomal amphotericin B (LAmB) in 531 patients with invasive candidiasis or candidaemia, with successful outcomes in 74% and 70% at EOT, but micafungin was better tolerated than LAmB [23]. In a three-armed study, intravenous micafungin (150 or 100 mg daily) was non-inferior to caspofungin (71% vs. 74% vs. 71% overall success, not significant (NS)) [24]. A recent randomized study reported no significant benefit of caspofungin at 150 mg daily as compared with 50 mg daily in patients with invasive candidiasis (80% vs. 72% overall success at EOT, NS) [25].

A comparative trial of intravenous itraconazole and fluconazole in 193 patients with candidaemia has reported similar success rates (67% vs. 69% overall success at EOT, NS), but this study was never published in full [26].

Response: On the basis of published clinical trial data, fluconazole (16 panellists) or an echinocandin (five panellists) were the most likely regimens to be selected for primary therapy of candidaemia in a stable, azole-naïve, mildly to moderately ill patient with uncomplicated sepsis (Fig. 1a).

In a recent comparative trial, anidulafungin was superior to fluconazole both in *C. albicans* and non-*albicans Candida* infections [22], favouring the use of echinocandins in severely ill patients. However, most panellists found that there were currently insufficient data to make an informed judgement on the potential superiority of anidulafungin or other echinocandins over fluconazole in mildly to moderately ill, stable, azole-naïve patients.

Only two panellists would use d-AmB as primary therapy. None of the panellists felt that itraconazole has a role in the treatment of invasive candidiasis, because of its potential for unfavourable drug interactions, drug-related adverse events, and the lack of published clinical trial data [27].

Although voriconazole proved to be equally effective as d-AmB [5], in clinical practice this drug was preferred as oral step-down therapy or for use in special cases where other antifungal agents were contraindicated.

It is of note that positive blood cultures are usually reported as positive for 'yeasts'. Although the most likely identity will be *Candida* species, the experts acknowledged that other yeasts, such as *Cryptococcus* and *Trichosporon* species, cannot be discounted, as they are not susceptible to echinocandins.

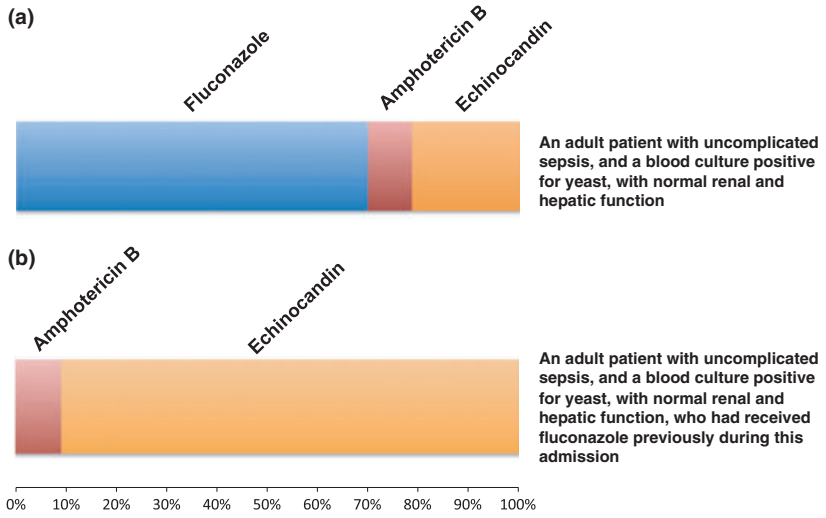

FIG. 1. Responses to the questions on initial treatment of candidaemic patients: (a) uncomplicated; (b) received fluconazole previously during this admission.

Is amphotericin B applicable in the treatment of adult patients with invasive candidiasis?

Background: Intravenous d-AmB has remained the reference standard for treating invasive fungal infections since its introduction in 1959, despite its acute infusion-related toxicity and nephrotoxicity. In comparative trials, the limited success rate of d-AmB was shown to be primarily attributable to its toxicity, leading to premature treatment discontinuations in many patients [5,20,28,29]. This was true even if d-AmB was given only for a median of 4 days, before stepping down to fluconazole [5].

Responses: The majority (14/22) of the panel felt that d-AmB no longer has a role in the therapy of invasive candidiasis, owing to the serious side effects associated with this drug. However, for second-line treatment of candidaemia, a lipid-based formulation of amphotericin B could be considered, despite the lack of comparative studies, with most favouring LamB, in view of the availability of recent data [23].

Which antifungal agent should be used to treat an adult, azole-naïve patient with candidaemia during a prolonged hospital stay?

Background: Most cases of nosocomial candidiasis are endogenous in origin and emanate from the patient's own gastrointestinal flora, although nosocomial transmission has been described [30]. Prolonged hospitalization is associated with a shift towards *Candida* species other than *C. albicans*, particularly after fluconazole prophylaxis [11,12]. Recent European studies have demonstrated increasing rates of decreased susceptibility to fluconazole in some but not all settings [7,18,31].

Responses: Two-thirds of the panel appeared to have no concerns about the increased risk of fluconazole resistance during a prolonged hospital stay, provided that patients had not been exposed to any azole therapy, and would use this drug as first-line therapy, as for a stable, hospital-naïve patient. One-third of the panel, however, preferred to use a broad-spectrum drug until species and susceptibility profiles have been established.

Which antifungal agent should be used to treat an adult patient with candidaemia who had received fluconazole previously during this admission?

Responses: Whereas there was no overall consensus on antifungal treatment for hospital-naïve or hospital-experienced patients, all panellists agreed that prior exposure to fluconazole would influence their choice of antifungal drug to cover possible fluconazole resistance; 21 would use an echinocandin, and only two would use d-AmB (Fig. 1b).

Which antifungal agent should be used to treat an azole-naïve, non-neutropenic, adult ICU patient with candidaemia?

Background: Medical and surgical ICUs have seen a substantial increase in the incidence of invasive candidiasis in recent years [4]. The emergence of *Candida glabrata* as a major pathogen among these patients [10] has been attributed to the increased use of fluconazole prophylaxis in ICU patients.

Responses: If an azole-naïve patient had uncomplicated sepsis and normal renal and hepatic function and was in an ICU, 13 of the 23 panellists indicated that they would still use fluconazole. However, most panellists acknowledged that the study on anidulafungin vs. fluconazole has suggested the superiority of echinocandins, even in less severely ill patients [22].

The presence of severe sepsis caused panellists to modify their approach to treatment. The majority (20) of the panel indicated that they would use an echinocandin rather than fluconazole (Fig. 2a); only two would use fluconazole in this setting. Although combined therapy with d-AmB plus fluconazole was more effective than high-dose fluconazole (800 mg daily) plus placebo at clearing *Candida* from the bloodstream of non-neutropenic adult patients with candidaemia [29], there was no enthusiasm for this combined regimen among the panel of experts, in view of the d-AmB-associated toxicity.

Choice of echinocandin: Currently, anidulafungin, caspofungin and micafungin are available in most European countries. The panellists noted very little difference in overall efficacy between these agents during the discussion at the conference, and this view was confirmed during subsequent discussions and review of this manuscript. More recently, the EMA, but not the FDA, has issued a caution that micafungin should only be used if other antifungals are not appropriate, as rat experiments (but not data from humans) suggested a potential risk for the development of liver tumours (http://www.ema.europa.eu/humandocs/Humans/EPAR/mycamine).

Which antifungal drug should be used to treat an adult neutropenic haematology patient with candidaemia, who had not received azole prophylaxis?

Background: LAmB, voriconazole and caspofungin have been investigated for the empirical treatment of haematological patients with unexplained fever during prolonged neutropenia [32–34]. *C. glabrata* and *Candida krusei* are more prevalent in haematology patients [3], and infection with these species may be refractory to fluconazole treatment. However, no comparative studies have been specifically performed in neutropenic patients with culture-proven candidaemia, and published studies have included very few neutropenic cases [20,22–24], precluding any conclusions on the efficacy of specific antifungal regimens for candidaemia in these patients.

Responses: If a patient had uncomplicated sepsis and normal renal and hepatic function, 13 panellists indicated that

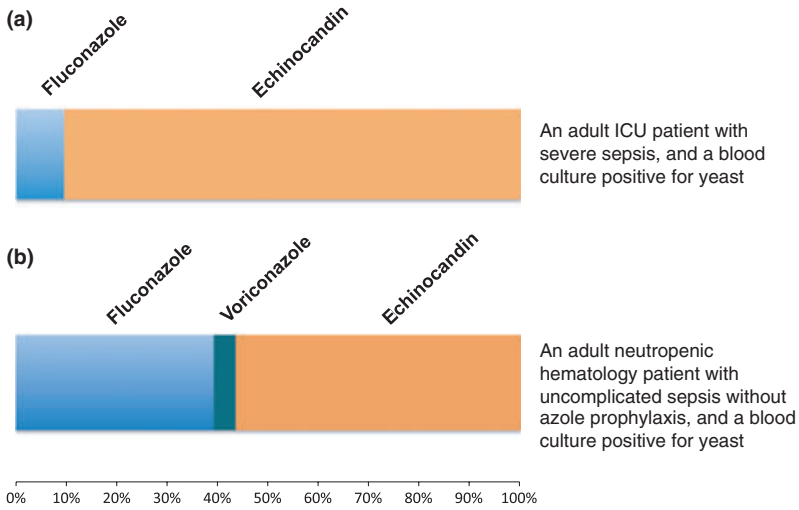

FIG. 2. Responses to the questions on initial treatment of candidaemic patients: (a) in the intensive-care unit (ICU) with severe sepsis, unstable or moderately to severely ill; (b) neutropenic haematology patient without azole prophylaxis.

they would use an echinocandin, nine would use fluconazole, and one would use voriconazole (Fig. 2b). It is of note that voriconazole and anidulafungin are not currently licensed for this indication in Europe.

Follow-on treatment or treatment in specific cases

What would be the choice of antifungal drug for an uncomplicated adult patient with fluconazole-susceptible C. albicans candidaemia?

Background: Antifungal susceptibility testing methods include those of the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST-AFST), as well as the commercial Etest. Not only do the CLSI and EUCAST-AFST differ in their breakpoints for fluconazole and voriconazole, but the EUCAST-AFST states that *C. glabrata* and *C. krusei* are not considered to be good targets for fluconazole, and there is as yet insufficient evidence to establish reliable breakpoints for voriconazole for those species [35,36]. In addition, the CLSI adopts the category of susceptible-dose-dependent to allow for dosage increases. Echinocandin resistance of *Candida* has been increasingly reported over the last few years, and is associated with various hot spot mutations in the FKS target gene [37–39]. In general, a median of 3 weeks of exposure has preceded the development of resistance, which has not been reported for echinocandin-naïve patients [38,39]. The isolates are characterized by elevated MICs for all available echinocandin agents, cross-resistance in animal infection models, and breakthrough infections in patients. Consequently, alternative drug classes are recommended to treat those cases [39–41].

Responses: All panellists favour fluconazole (400 mg daily) in a stable, uncomplicated patient once they know that the *C. albicans* is susceptible. Even in a patient who was responding to an echinocandin, all 23 panellists indicated that they would switch to fluconazole as long as the patient had become stable and the isolate was sensitive, in view of the lower costs and oral availability of fluconazole. These results underscore that all panellists recommended an active step-down approach to streamline antifungal therapy as soon as the patient had stabilized and the species and susceptibility had become available. As mentioned above, panellists acknowledged that the study on anidulafungin vs. fluconazole may shed new light on the comparative efficacies of fluconazole and echinocandins in the future, even in haemodynamically stable patients [22].

What would be the choice of antifungal drug for an uncomplicated adult with C. glabrata candidaemia?

Responses: Even if the *C. glabrata* isolate was demonstrated to be fluconazole-susceptible *in vitro*, most panellists were concerned about using fluconazole for a *C. glabrata* infection. Over 50% of panellists favoured using an echinocandin, whereas five indicated that they would increase the fluconazole dose to 800 mg daily. Only five panellists indicated that they would be prepared to use fluconazole at a dose of 400 mg daily (Fig. 3a).

However, if the patient had been started on fluconazole (400 mg daily) and was stabilized and doing well at the time when species and susceptibility became known, seven of 24 panellists were inclined to continue treatment, but the majority would either increase the dose to 800 mg daily or higher or switch to another agent. Seven of the panellists would prefer to switch to an echinocandin, and one favoured voriconazole, regardless of the clinical status of the patient. If fluconazole was continued, the panellists agreed that the

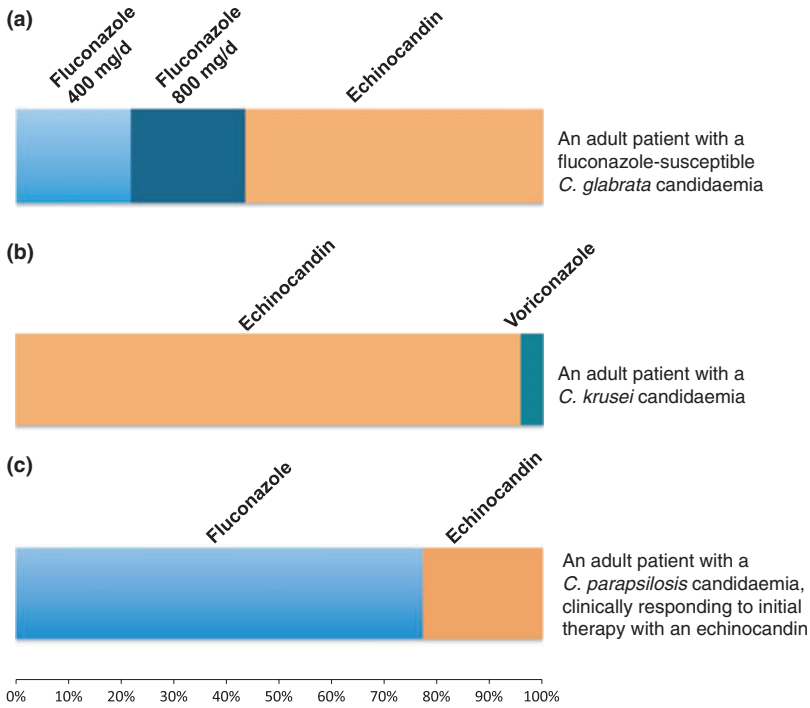

FIG. 3. Responses to the questions on treatment of candidaemic patients (a) infected with fluconazole-susceptible *Candida glabrata*; (b) infected with *Candida krusei*; or (c) infected with *Candida parapsilosis* and clinically responding to initial therapy with an echinocandin.

patient's condition should be monitored closely for any signs of clinical deterioration, which may initiate a switch to an alternate antifungal.

What would be the choice of antifungal drug for an uncomplicated adult patient with C. krusei candidaemia?

Responses: As *C. krusei* is inherently resistant to fluconazole, most of the panellists (22/23) indicated that they would use an echinocandin, and one would use voriconazole (Fig. 3b).

What would be the choice of antifungal drug for a responding adult patient started on caspofungin who is infected with C. parapsilosis?

Background: The correlation between MICs and *in vivo* response is less clear for the echinocandins than for fluconazole, and interpretive breakpoints have been more difficult to establish. Echinocandin drugs consistently show higher MICs for *C. parapsilosis* than for other *Candida* species [40,42], and there are reports of increased clinical failure and persistence of infection with this species [20,22,25,43–45].

Responses: Interestingly, most of the panel felt that this issue should be taken at least as seriously as *C. glabrata* fluconazole resistance; only five panellists indicated that they would continue with an echinocandin, whereas 17 of 22 would switch to another class of antifungal drug, even if the susceptibility of the strain was within the range usually considered to be susceptible *in vitro* (e.g. MIC of 1 mg/L). If the patient was not responding to an echinocandin at all, all 23 panellists indicated that they would switch the class of antifungal drug and use an azole compound.

What are the indications for primary combined therapy with two antifungal agents in invasive candidiasis?

Background: Antifungal combination therapy has been advocated in a few specific areas, e.g. *Candida* endocarditis. Combined medical and surgical approaches, including surgical removal of infected heart valves or implanted devices and debridement of infected perivalvular tissue, are essential to the successful management of *Candida* endocarditis. Combined antifungal therapy regimens including flucytosine have been recommended for *Candida* endocarditis, endophthalmitis, and central nervous system infections, as flucytosine penetrates well into all body tissues, including cerebrospinal fluid, and has documented synergistic activity with amphotericin B [46].

Responses: The majority of the panellists agreed that there are currently no proven indications for primary combination therapy in adult patients with invasive candidiasis (Fig. 3c). However, for *Candida* endocarditis, several panellists indicated that they would use combination therapy with either a lipid-associated amphotericin B plus flucytosine (five votes) or an echinocandin plus flucytosine (eight votes).

For a patient with a cerebral *Candida* infection, many would use fluconazole (eight votes) or voriconazole (five votes), whereas ten favoured combined therapy, mostly lipid-associated amphotericin B + flucytosine. The choice of voriconazole was mainly based on extrapolation from the many case reports in the literature on the successful management of cerebral aspergillosis with voriconazole [47]. None of the panellists would recommend echinocandin monotherapy for cerebral candidiasis; penetration of this drug into the central nervous system was thought to be insufficient, and most panellists felt that there was a lack of data to support this indication.

On the basis of published data, what is the role of efungumab?

Background: Efungumab (trade name: Mycograb) is a human recombinant monoclonal antibody against heat shock protein 90 with antifungal activity *in vitro*. It is not currently approved anywhere in the world, but it was under development at the time of this conference, and its potential role was discussed. In a randomized comparison of lipid-associated amphotericin B plus efungumab vs. lipid-associated amphotericin B plus placebo in 139 patients with candidiasis, significantly better outcome was reported for efungumab plus amphotericin B than for amphotericin B plus placebo (complete overall response by day 10, 84% vs. 48%, respectively; $p < 0.001$). No serious side effects were reported in the publication [48].

Responses: Although the majority of the panellists felt that immunotherapy was potentially interesting, the only published trial was unconvincing, and concerns were expressed about some aspects of the study design and report. The panellists' consensus was that the study raised many unanswered questions, including patient selection, assessment of endpoints, blinding, independent data review, adverse effects, and even potentially increased mortality in the efungumab group [48,49]. After in-depth discussion, the majority of panellists indicated that they would not consider using efungumab for the time being, as there are insufficient data available to support its use.

Follow-up and management of patients

Would you obtain follow-up cultures after the start of therapy in patients with candidaemia?

Background: The Practice Guidelines for the Treatment of Candidiasis published by the Infectious Diseases Society of America (IDSA) [50] recommend that treatment of candidaemia be continued for 2 weeks after the last positive blood culture has been obtained and resolution of signs and symptoms of infection has occurred. However, these cultures are infrequently obtained, and there are currently no recommendations to obtain follow-up cultures in any official guidelines. In clinical practice, physicians seldom seem to follow the guideline to base duration of treatment on the course of blood culture positivity [51].

Responses: All of the panellists indicated that they would perform follow-up cultures after the start of therapy, although six indicated that they would not do this for every single patient. This is in line with the treatment guidelines mentioned above, which relate duration of treatment to the last positive blood culture. Although there was no formal vote on the subject of treatment duration in candidaemia and invasive candidiasis, it was agreed that clinicians should follow the guidelines proposed by the IDSA [50].

Should ophthalmoscopy be performed on patients with candidaemia?

Background: The incidence of *Candida* endophthalmitis or chorioretinitis in patients with candidaemia has been reported to range from 5% to 78% [52,53]. In a large series of 370 non-neutropenic candidaemic patients who prospectively underwent repeated ophthalmoscopy [5], 16% had ocular involvement, and in 9.5% this was probably or definitely caused by *Candida*. The IDSA treatment guidelines recommend that all patients with candidaemia should undergo ophthalmoscopy, including a dilated retina examination [50].

Responses: Eighteen panellists indicated that it was important to carry out ophthalmoscopy, whereas four thought that ophthalmoscopy was not indicated, as the antifungal drugs used to treat candidaemia would clear the ocular site as well; however, the panel felt that this was less likely with the echinocandins than with azole drugs. Ophthalmoscopy should not be performed too early, as lesions may become visible during therapy; it was agreed that ophthalmoscopy should be carried out before antifungal treatment is stopped, to enable a decision to prolong treatment if required.

Should intravenous catheters be removed if feasible?

Background: Indwelling intravenous catheters do not necessarily represent the origin of candidaemia, but may act as a reservoir of infection that may prolong candidaemia and lead to metastatic foci of infection. Early removal of central venous catheters from patients with bloodstream infection has been considered to be essential to successful patient management [54] and is currently recommended in the IDSA guidelines for candidaemia [50]. Exchange of a catheter at the original site over a guide wire was thought not to be beneficial [54]. A recent literature review found that only one study revealed a definite benefit of catheter removal in neutropenic patients with candidaemia [55], and a large analysis was unable to demonstrate a beneficial effect of early

catheter removal in candidaemic patients treated with an echinocandin or LAmB [56]. It has been recommended that the benefits of catheter removal should be weighed carefully against the risks for each patient [57].

Responses: Despite the paucity of data on catheter management and proof of the perceived benefits of catheter removal, all panellists indicated that removal of intravascular catheters should be considered in a patient with candidaemia, and 20 of 22 indicated that these catheters should be removed if feasible.

Panellists had differing views about the minimum required time interval between central catheter removal and insertion of a new catheter at a new body site, although most (16/23) indicated that a new catheter could be inserted straight away and that no delay was necessary. It is important that antifungal therapy be started before catheter exchange, and, in the presence of an antifungal in the bloodstream, most panellists felt that subsequent biofilm formation and colonization of the new catheter would be prevented even if it was inserted without a catheter-free interval.

Prophylaxis and empirical therapy in the ICU

Are there any ICU patients for whom prophylaxis is routinely indicated?

Background: Patients in ICUs have a high risk of developing invasive candidiasis, which increases with the length of ICU stay. Studies on prophylaxis with fluconazole have shown a reduction in the incidence of invasive *Candida* infections but not an improvement in survival in selected subsets of high-risk ICU patients [58–60]. Antifungal prophylaxis should be targeted at specific patients at high risk of developing candidiasis [61], and various selection rules have been proposed to identify such patients [62].

Responses: Most panellists (18/21) felt that prophylaxis was indicated for some ICU patients. All of the prophylaxis trials to date have considered highly selected subsets of populations, and none of the studies has addressed the general ICU population. All experts felt that high-risk solid organ transplantation (liver or kidney–pancreas) is the most important factor requiring anti-*Candida* prophylaxis. Other risk factors that would make the panellists consider antifungal prophylaxis included major abdominal surgery, new renal failure requiring haemodialysis/haemofiltration, total parenteral nutrition, prolonged use of broad-spectrum antibiotics, and prolonged ICU stay. As these factors are present in many ICU patients, it was felt that they should not be considered as indications for prophylaxis until a well-validated decision rule is available, and that further studies are required to identify specific high-risk groups so that antifungal prophylaxis can be targeted to those who will most benefit from it.

Are there any subsets of ICU patients for whom empirical therapy is indicated, and which risk factor would prompt intensivists to initiate empirical anti-Candida therapy?

Background: The IDSA guidelines state that empirical therapy should be administered only to febrile patients with *Candida* colonization (preferably at multiple sites) and multiple other risk factors in the absence of any other demonstrable cause of fever [50]. However, only about half of the ICU patients with candidaemia are known to be colonized at the time when the infection is diagnosed, mostly because they acquire candidaemia early during their ICU stay [62]. A randomized controlled trial of 800 mg/day fluconazole vs. placebo showed no overall benefit in 270 adult ICU patients with fever despite administration of broad-spectrum antibiotics [63]. Nevertheless, retrospective studies demonstrating a strong correlation between delay in the start of antifungal therapy and mortality in candidaemic patients [14,15] suggest that early empirical therapy in patients at high risk of having candidaemia may be beneficial.

Responses: The large majority of panellists (22/24) agreed that empirical therapy is indicated in some subsets of ICU patients. In identifying those ICU patients with unexplained sepsis or septic shock (not just unexplained fever) who may benefit from early empirical antifungal therapy while blood culture results are pending, the panellists identified several important risk factors: colonization at other body sites was considered to be the most important risk factor (19 responses), and major abdominal surgery was also considered to be important (12 responses), as were positive catheter tip cultures (16 responses), although not justifying empirical therapy if present as a single risk factor [64]. Prolonged ICU stay, prolonged use of broad-spectrum antibiotics, the presence of a central line and haemodialysis/haemofiltration were considered to be less important. These responses are in agreement with a recent cohort study in Spain, which identified similar risk factors [65,66]. Only 12 panellists indicated that they carried out surveillance cultures for *Candida* in ICU patients, and 14 did so in neutropenic patients, whereas the others did not carry out surveillance cultures routinely.

Diagnosis of invasive candidiasis

What is the clinical utility of the β-D-glucan assay?

Background: The diagnosis of invasive candidiasis relies essentially on the culture of blood and other specimens from normally sterile body sites. Several tests to detect *Candida* antigens or antibodies are now available commercially (CandTec, Pastorex *Candida*, Platelia *Candida* Ag (BioRad, Marnes-la-Coquette, France); Fungitec G-test (Seikagaku, Tokyo, Japan); Fungitell (Associates of Cape Cod, East Falmouth, MA, USA)). Tests for the detection of *Candida*

mannan (Pastorex *Candida*; Platelia *Candida* Ag) and anti-mannan antibodies have been explored in different patient populations [67], but have shown variable sensitivity and specificity in patient groups including surgical and ICU patients [67–70]. Tests for the measurement of serum (1 → 3)-β-D-glucan (Fungitec G-test; Fungitell) are not specific to *Candida* infection, as they detect β-D-glucan from many fungal pathogens, including *Aspergillus* spp. and *Fusarium* spp. [68,71]. However, detection of β-D-glucan may be a useful adjunct for the diagnosis of candidiasis in addition to other indicators of infection [66].

Responses: Only six panellists indicated that they would use the β-D-glucan assay in selected patients, and 15 indicated that there was insufficient evidence from clinical studies to support the use of this assay routinely. Panellists felt that the lack of a control 'at-risk' population in the above studies precludes a definitive judgement on the predictive value of the test in clinical practice, and there were concerns about the high rate of positive results in patients with other fungal infections.

Most panellists considered the incidence of candidaemia to be too low to justify the expense of the β-D-glucan test. They also felt that a negative mannan test result and a negative β-D-glucan test result may be more useful for exclusion of a diagnosis of candidaemia than a positive result would be for the initiation of therapy.

Summary

All panellists participating in this European consensus conference agreed on the need for early intervention in candidaemia and the need to treat all patients with candidaemia. Despite the conflicting data [56], there was also a consensus that central intravenous lines should be changed wherever possible, with most but not all panellists agreeing that a new line can be inserted straight away. Overall, there was no consensus on the most effective antifungal strategy, but there was an obvious swing away from amphotericin B, because of drug-related toxicity. Panellists strongly agreed that treatment strategies need to be modified on an individual patient basis, depending on local epidemiological data, degree of immune compromise, history of recent azole exposure, and severity of illness. Most panellists favoured an echinocandin in moderately or severely ill patients with candidaemia, those recently exposed to azole drugs, and those with *C. glabrata* or *C. krusei* infection. Although anidulafungin was found to be superior to fluconazole in a recent comparative candidaemia trial [22], most panellists felt that there were currently insufficient data available to judge the potential superiority of echinocandins over fluconazole in mildly ill, stable, azole-naïve patients. Although most panellists agreed that there is currently no indication for primary combination therapy in candidaemia, a number of the panellists felt that combination therapy was useful for cerebral *Candida* infections and endocarditis.

Although serological methods can provide an early diagnosis of infection before blood culture results are known, most experts felt that these assays do not have sufficient sensitivity or specificity to influence their clinical decision-making.

Most panellists agreed that antifungal prophylaxis in ICU patients is indicated in some but not all patients. As in previous published studies [61,62,65], panellists felt that further work was necessary to identify precisely which subsets of patients would benefit the most from antifungal prophylaxis. There was also agreement that empirical therapy would be useful in some subsets of ICU patients with unexplained sepsis. *Candida*-positive catheter tips, colonization at multiple body sites and major abdominal surgery were considered to be the principal risk factors for candidaemia justifying empirical therapy in septic patients.

The data from this European expert consensus document show that the introduction of a number of new antifungal drugs has served to facilitate a more tailor-made approach to antifungal therapy. Further clinical trials are required to compare different antifungal treatment regimens in specific patient populations, in order to determine the most effective treatment strategy for defined subsets of patients. Until these have been carried out and data are available to demonstrate clinical superiority of one antifungal drug over another, antifungal treatment needs to be modified on an individual patient basis and should be guided by local experience.

Conflicts of Interest

The meeting was funded by an unrestricted grant from Pfizer (The Netherlands). The sponsor was not involved in the selection of participants or procedures, or in the discussion, data collection, analysis, or writing of the manuscript. All authors had full access to all the data in the study, and the corresponding author held final responsibility for the decision to submit the publication.

Transparency Declaration

Bart-Jan Kullberg has received funds for speaking, consultancy, advisory board membership, travel from Astellas,

Gilead, Pfizer; and has received research funding from BioMérieux.

Paul Verweij has received research funding from Pfizer, Merck, Basilea, Schering Plough, Cephalon, Biorad, Gilead.

Murat Akova has received funds for speaking, consultancy, advisory board membership, travel from Gilead, Pfizer, Wyeth, Merck; and has received research funding from Pfizer, Merck, Wyeth.

Maiken Arendrup has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Cephalon, Gilead, Merck, Pfizer, Schering Plough, Swedish Orphan; and has received research funding from Pfizer, Merck.

Thierry Calandra has received funds for speaking, consultancy, advisory board membership, travel from Merck, Novartis, Pfizer.

Manuel Cuenca Estrella has received funds for speaking, consultancy, advisory board membership, travel from Gilead, Merck, Pfizer, Schering Plough; and has received research funding from Astellas, Biomerieux, Gilead, Merck, Pfizer, Schering Plough, Soria Melguizo SA.

Raoul Herbrecht has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Cephalon, Gilead, Merck, Novartis, Pfizer, Schering Plough; and has received research funding from Pfizer.

Frédérique Jacobs has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Pfizer, Merck, Schering Plough.

Mats Kalin has received research funding from Wyeth.

Chris Kibbler has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Gilead, Merck, Pfizer, Schering Plough; and has received research funding from Gilead, Merck.

Olivier Lortholary has received funds for speaking, consultancy, advisory board membership, travel from Merck, Pfizer, Schering Plough, Gilead.

Jacques Meis has received funds for speaking, consultancy, advisory board membership, travel from Basilea, Cephalon, Merck, Pfizer, Schering Plough; and has received research funding from Astellas.

Patricia Munoz has received funds for speaking, consultancy, advisory board membership, travel from Gilead, Merck, Pfizer, Schering Plough; and has received research funding from Schering Plough.

Frank C Odds has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Gilead, Merck, Pfizer, Italfarmaco, Novabiotics, Johnson & Johnson Pharmaceutical Research; and owns stocks or shares in Johnson & Johnson.

Ben de Pauw has received funds for speaking, consultancy, advisory board membership, travel from Gilead Basilea .

John Rex is (was) an employee of AstraZeneca Pharmaceuticals; and owns stocks or shares in AstraZeneca Pharmaceuticals.

Emmanuel Roilides has received funds for speaking, consultancy, advisory board membership, travel from Cephalon, Enzon, Gilead, Merck, Pfizer, Sanofi-Aventis Astellas, Schering Plough, Wyeth; and has received research funding from Pfizer, Gilead, Schering Plough.

Thomas Rogers has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Gilead, Merck, Pfizer, Schering Plough; and has received research funding from Merck.

Marcus Ruhnke has received funds for speaking, consultancy, advisory board membership, travel from Basilea, Gilead, Merck, Novartis, Pfizer, Pliva, Schering Plough; and has received research funding from Pliva, Pfizer.

Andrew Ullman has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Basilea, Merck, Pfizer, Schering Plough.

Ömrüm Uzun has received research funding from Merck, Basilea, Pfizer.

Jean-Louis Vincent has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Merck, Pfizer, Schering Plough.

J Peter Donnelly has received funds for speaking, consultancy, advisory board membership, travel from Astellas, Basilea, Gilead, Merck, Pfizer, Schering Plough; and has received research funding from Gilead, Merck, Pfizer, Schering Plough.

Jacques Bille and Koenraad van de Woude have no conflicting or dual interests to declare. Please note that Prof. Pietro Martino has sadly died in 2007.

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