EXPERT REVIEWS

Current pharmacological concepts for wise use of echinocandins in the treatment of *Candida* infections in septic critically ill patients

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Candida infections represent challenging causes of severe sepsis and/or of septic shock in the critically ill patients. Knowledge of current pharmacological concepts may promote a more wise use of echinocandins in the management of *Candida* infections in this setting. Echinocandins have some advantages over azoles, both pharmacodynamically (rapid fungicidal activity, anti-biofilm activity, unmodified activity against *Candida* isolates with decreased susceptibility to azoles and anti-cytokine/anti-chemokine activity) and pharmacokinetically (low interindividual variability, low potential for drug–drug interactions), that may influence the timing and the choice of therapy of *Candida* diseases in the critically ill patients. However, concerns exist in regards to the feasibility of fixed dosing regimens of echinocandins in all of the different patient populations and in regards to the effectiveness of echinocandin monotherapy in some clinical settings. In presence of deep-seated infections, voriconazole or liposomal amphotericin B may be valuable alternatives or add-on therapy.

Keywords: candidemia • candidiasis • clinical pharmacology • critically ills • echinocandins

Candida infections represent frequent and challenging causes of severe sepsis and/or of septic shock in the non-neutropenic critically ill patients, and are associated with considerable morbidity and mortality [1–3]. Fluconazole has represented the mainstay of treatment of *Candida* infections in the past decade. However currently, the echinocandins are the first-line antifungal agents which are recommended in this setting by both the guidelines of the Infectious Diseases Society of America (IDSA) [4] and those of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [5].

Knowledge of current pharmacological concepts may promote a more wise use of these antifungal agents in this setting, with the intent of both maximizing clinical cure rates and preserving the activity over time by avoiding the spread of echinocandin resistance.

There are several pharmacodynamic characteristics that support the primary role of echinocandins over fluconazole in the therapeutic management of severe *Candida* infections in the critically ill patients (**Box 1**).

Pharmacodynamic advantages of echinocandins over fluconazole in the management of *Candida* infections in septic critically ill patients

Rapid candidacidal activity

Several experimental animal models of infection have shown that echinocandins exhibit rapid fungicidal activity against *Candida*. In this regard, in a neutropenic murine model comparing the efficacy of anidulafungin and caspofungin with that of fluconazole in terms of fungal burden reduction after 24 h of treatment, it was shown that a significantly higher

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Box 1. Pharmacodynamic advantages of echinocandins versus fluconazole in treating *Candida* infections in the critically ill patients.

- Rapid fungicidal activity
- Anti-biofilm activity
- Unchanged activity against *Candida* spp. showing decreased susceptibility to fluconazole and to other azoles
- Anti-cytokine and anti-chemokine activity

decrease of CFU occurred in the kidney of the echinocandin-treated mice compared with that of the fluconazole-treated mice (>2 vs 1.2 $\log_{10}$ CFU; $p < 0.003$). This rapid candidacidal activity of echinocandins led the authors to suppose that this class of antifungals may contribute to an improved outcome in critically ill patients [6].

Interestingly, several recent clinical studies support this hypothesis. In a prospective study assessing the influence of antifungal treatments on the outcome of 433 episodes of candidemia, which were divided into two subsequent time periods according to the introduction of echinocandin treatment (1994–2003 [A] and 2004–2008 [B]), a significantly lower mortality rate was observed in period B compared with period A (27 vs 36%; $p = 0.03$). Additionally, echinocandin use, alone or in combination therapy, was associated with better outcome (odds ratio [OR]: 0.22; 95% CI: 0.06–0.81; $p = 0.02$) [7].

In a *post-hoc* analysis of a prospective randomized clinical trial of anidulafungin versus fluconazole for the treatment of invasive candidiasis [8], which was aimed to assess the outcome in the subset of patients with critical illness (defined as the presence of at least one criteria among APACHE II score ≥15, evidence of severe sepsis and/or patient in intensive care), global response rate with anidulafungin (n = 89) was higher than with fluconazole (n = 74; 70.8 vs 54.1%; $p = 0.03$) [9].

A recent patient-level quantitative review of seven randomized clinical trials showed that treatment with an echinocandin antifungal was one of the two most relevant predictors of decreased mortality among 1915 patients with candidemia and other forms of invasive candidiasis (OR: 0.65; 95% CI: 0.35–0.72; $p = 0.0001$) [10].

These studies clearly suggest that treatment with an echinocandin may improve clinical response in severe critically ill patients with *Candida* infections. However, it should not be overlooked that in septic critically ill patients also time of initiation of appropriate antifungal therapy may be relevant.

In this regard, a multicenter retrospective study was focused at evaluating the impact of timing of caspofungin administration on time to clinical stability among non-immunocompromised adult patients with invasive candidiasis. Of note, the number of days needed to achieve clinical stability in 50% of cases was significantly shorter in patients receiving early treatment (within 3 days from the time the sample for culture was taken, n = 107) than in those receiving delayed therapy (n = 62; 7 vs 13 days; $p < 0.0001$) [11].

In a recent retrospective analysis of 224 patients with septic shock attributed to *Candida* infection, appropriate antifungal therapy started within 24 h of the onset of shock was associated with a greater likelihood of survival ($p < 0.001$) [2]. Interestingly, when looking at the different classes of antifungals which were considered appropriate in terms of spectrum of activity, initial antifungal treatment with an echinocandin resulted more frequent among lived (n = 69) than among died (n = 155; 69.8 vs 49.0%; $p < 0.001$), whereas treatment with azoles (fluconazole or voriconazole) was almost equally distributed in the two groups (18.8 vs 16.1%) [2].

Overall, these studies support the contention that early administration of an echinocandin is effective for the treatment of severe *Candida* infections in critically ill patients with severe sepsis or with septic shock, in agreement with the recommendations of the IDSA guidelines [4].

Anti-biofilm activity

Another relevant pharmacodynamic property of the echinocandins is the anti-biofilm activity.

Candida spp. has a great propensity to colonize intravascular catheters and to produce biofilm on luminal surface, and this, by favoring the persistence of yeast reservoir, is a relevant risk factor for catheter-related candidemia [2,10]. A recent study assessing the propensity of biofilm formation among 393 clinical isolates of *Candida* species causing bloodstream infection showed that the ability to produce biofilm may greatly vary among *Candida* species. Of note, only 40% of the *C. albicans* isolates formed biofilm compared with 88.7% of the non-*albicans* isolates ($p < 0.0001$) [12]. Among the latter, *C. tropicalis* and *C. lusitaniae* were the most efficient biofilm producers (100%), followed by *C. glabrata* (95%), *C. dubliniensis* (85.7%) and *C. parapsilosis* (66.7%) [12].

Noteworthy, the anti-biofilm activity is a property of the echinocandins which was not shown to be shared by the triazoles. In an *in vitro* study, the anti-biofilm activity of anidulafungin and caspofungin was compared with that of voriconazole and posaconazole against *C. albicans* and *C. parapsilosis*. Whereas the MICs against biofilm-embedded *Candida* strains (defined as the concentration needed to obtain a 50% reduction in the metabolic activities of biofilms in an XTT colorimetric assay) were in the range of therapeutic concentrations for the echinocandins (≤1 mg/l for caspofungin and ≤2 mg/l for anidulafungin), this was not the case for triazoles, which neither at supra-therapeutic concentrations (≥64 mg/l) exhibited any anti-biofilm activity [13]. Interestingly, it was shown that the mechanisms of biofilm-mediated resistance against azoles are probably mediated by β-1,3-glucan synthesis and deposition in the matrix. This carbohydrate may trap the azole drug, thus preventing its intracellular action [14].

Although prompt catheter removal in candidemic patients is often considered mandatory for adequate source control [2,10], however, some controversy on this approach still exists [15]. Additionally, it should be noticed that device removal cannot always be assured promptly, as, for example, in case of

implantable catheters and/or of vascular prosthesis. On the basis of the aforementioned studies, it may be speculated that the anti-biofilm activity of the echinocandins may be extremely valuable in these cases, especially when the infection is sustained by high-biofilm producing strains of non-*albicans* species of *Candida*. However, it should not be overlooked that in these cases even the lipid formulations of amphotericin B might be helpful, since they have also been hypothesized to be active against biofilm [16,17].

Interestingly, it was recently highlighted that the anti-biofilm activity of the echinocandins may be potentiated by the NSAIDs [18]. In a catheter-associated *C. albicans* biofilm rat model, significantly fewer biofilm cells were found in catheters retrieved from animals treated with caspofungin plus diclofenac in comparison with those retrieved from animals treated with each drug alone. The findings were attributed to a diclofenac-induced increase of the membrane permeability of the biofilm cells and/or to a potential alteration of the biosynthesis of fungal prostaglandins. On this basis, it was suggested that coating of medical devices, such as implants and plastics, with diclofenac can, in combination with conventional antifungal therapy, be envisaged for the eradication of *C. albicans* biofilm [18]. Additionally, considering the common use of diclofenac in intensive care units for fever treatment [19,20], it may be speculated that critically ill patients who receive caspofungin for the treatment of *Candida* biofilm-associated infections while on treatment with diclofenac for fever control, could benefit from this drug combination.

Unmodified activity against Candida *isolates with decreased susceptibility to fluconazole*

Another important pharmacodynamic property of the echinocandins is the maintenance of valid activity against *Candida* isolates with decreased susceptibility to fluconazole and to their azoles.

Fluconazole continues to be widely used in the hospital setting both for prevention and for treatment of fungal infections [21]. It was documented that previous fluconazole-exposure may represent a risk factor for selecting fluconazole-resistant *Candida* strains [22]. Worryingly, the reduced susceptibility of *Candida* to fluconazole is frequently coupled with a consensual decrease in that of the other azoles [23], and this might hamper the role of the whole azole class in the treatment of fluconazole-resistant *Candida* infections.

Conversely, the echinocandins usually maintain unchanged activity against these isolates [23], and this means, from a clinical standpoint, that they may represent a valuable rescue strategy for fluconazole-resistant *Candida* infections and an effective treatment of *Candida* infections in settings where fluconazole prophylaxis has been adopted.

Anti-cytokine & anti-chemokine activity

One of the major problems of patients with severe *Candida* infections is the appearance of severe sepsis or of septic shock during fungal infection [2]. This, by promoting uncontrolled generalized inflammatory response with cytokine storm, may induce universal endothelium injury, and cause multiple organ dysfunction syndrome, with subsequent death [24,25].

In this regard, it was recently highlighted that the echinocandins may inhibit cytokine and chemokine production, differently from what occurs with other classes of antifungal agents [26,27]. This was demonstrated in an *in vitro* model of human monocytes activated by *C. glabrata* infection, in which the anti-cytokine and anti-chemokine activity of various classes of antifungal agents was assessed. Echinocandins, at high but therapeutically achievable concentrations (7.5 mg/l for micafungin and anidulafungin, 12 mg/l for caspofungin), inhibited mainly the production of TNF-α and IL-1β ($p < 0.01$), and, to a variable extent, also that of other cytokines/chemokines (IL-1ra, IL-6, IL-8, IL-10, MCP-1, MIP-1β). Conversely, voriconazole or amphotericin B alone had little or no inhibitory effect on cytokine and chemokine production [26]. On the basis of these findings, it was hypothesized that echinocandins, by counteracting cytokine storm, might improve host survival in patients with severe *C. glabrata* infection characterized by inappropriate generalized inflammatory response [26].

Of note, this might open new therapeutic perspectives for the echinocandins in *C. glabrata* infections. In this regard, it's worth noting that, in a recent review of seven randomized clinical trials of severe *Candida* infections, when exploring the secondary composite success end point in the *C. glabrata* subgroup, treatment with an echinocandin remained associated with increased response [10].

However, it should not be overlooked that echinocandins were also shown to enhance pro-inflammatory effects against *Candida* species through beta-glucan unmasking, this favoring fungal killing by neutrophils and macrophages [28,29].

Unresolved pharmacodynamic issues of echinocandins: could the three echinocandins have different profiles of efficacy in the treatment of *Candida* infections?

An unresolved question is whether or not the three echinocandins may represent useful alternatives in clinical practice [30].

Although nowadays no definitive answer to this question still exists, however some experimental data seem to suggest that the activity of anidulafungin, caspofungin and micafungin may be similar in the treatment of infections sustained by *C. albicans*. In this regard, in a neutropenic murine disseminated candidiasis model it was shown that the profiles of the best fit lines describing the decrease of the kidney fungal burden in relation to the AUC/MIC ratio after 4 days of treatment were almost overimposable for the three echinocandins against *C. albicans* [31]. Conversely, in the same model, the three echinocandins exhibited different profiles against *C. glabrata* and *C. parapsilosis*.

Likewise, different profiles were observed for the three echinocandins when assessing the efficacy against *C. parapsilosis*, *C. orthopsilosis* and *C. metapsilosis* after 6 days of therapy at 5 and 10 mg/kg/day in another neutropenic murine model of disseminated candidiasis. Interestingly, caspofungin was the only

echinocandin that significantly decreased the kidney fungal burdens of all the tested strains, whereas micafungin was effective only against *C. metapsilosis,* and anidulafungin resulted ineffective [32].

These different profiles of efficacy for the three echinocandins in experimental animal models of non-albicans *Candida* infections [31–33] seem promising from the clinical point of view. Clearly, further studies are needed to predict treatment success in clinical practice, but it could be hypothesized that these differences could be especially valuable for *C. parapsilosis* infections, considering that the very low *in vitro* susceptibility of this species of *Candida* to echinocandins (100-fold lower than other species) generated concerns about the role of echinocandins in this setting, and lead the experts drawing up the IDSA guidelines in 2009 to favor fluconazole over echinocandins [4].

Unresolved pharmacokinetic issues of echinocandins

From a pharmacokinetic point of view, echinocandins are characterized by low interindividual variability and by low potential for drug–drug interactions [34]. This is because elimination occurs mainly by slow degradation to inactive metabolites with minimal renal excretion as unchanged moiety, and because these antifungals are poor substrates for, or do not inhibit or induce cytochrome P450 (CYP) enzymes, and neither are substrates for the P-glycoprotein transport systems [34].

Although this supports the assumption of an ease of use for the echinocandins in the critically ill patients, that is further supported by the better safety profiles of these agents with significantly fewer adverse events in comparison with those caused by other classes of antifungals [34], however some recent data suggest that the pharmacokinetics of the echinocandins may be significantly altered in some clinical settings.

Is fixed dosage always feasible for the echinocandins?

Two aspects of concern require attention and further insights, namely the fact that the echinocandins are used at dosages which are not adjusted to body weight, and that of the extensive plasma protein binding exhibited by these antifungals.

Both of these issues were highlighted in a recent open study assessing caspofungin exposure among 40 surgical ICU patients after administration of standard dosages. Of note, significantly lower plasma trough levels were predicted in patients with high body weight (>75 kg; $p = 0.019$) and in those with severe hypoalbuminemia (<23.6 g/l; $p = 0.030$) [35].

This suggests that dosages higher than the standard ones could be necessary for optimal exposure with echinocandins in obese patients and/or in those with severe hypoalbuminemia.

Indeed, the issue of echinocandin dosage in obese patients is being addressed, and currently caspofungin is the first echinocandin for which the maintenance dose has been augmented to 70 mg/day in patients weighing >80 kg [36].

Conversely, the issue of the negative influence that severe hypoalbuminemia might have on echinocandin exposure is still a matter of debate, with some observations suggesting its relevance and others not [37,38]. Overall, considering the rather frequent occurrence of severe hypoalbuminemia in patients with severe sepsis and/or with septic shock, these findings claim for the urgent need of pharmacokinetic studies of the three echinocandins in this patient population.

Could echinocandin monotherapy be inappropriate in some clinical pictures of deep-seated Candida *infections?*

A major pharmacokinetic issue of echinocandins is the limited diffusion through the anatomical barriers, due to the peptidic nature and to the very high molecular weight of these antifungal agents. Data on diffusion of echinocandins in various difficult-to-access compartments of the body come from some recent reports.

Candida empyema

Candida empyema is a serious complication of disseminated candidiasis. Anidulafungin is the only echinocandin for which penetration into pleural fluid was assessed during the treatment of a patient with *Candida* empyema. The $AUC_{pleural\ fluid}/AUC_{serum}$ ratio was relatively low (12.5%), and absolute pleural fluid concentrations ranged from 0.67 to 0.88 mg/l. Accordingly, it was concluded that *Candida* species with an MIC of ≥1 mg/l would likely not be eradicated from the pleural space, and that alternative antifungal agents with better pleural diffusion, such as voriconazole [39] or liposomal amphotericin B [40], would be warranted.

Candida peritonitis

The incidence of *Candida* peritonitis is increasing and the mortality rate remains high [41]. Of note, no data about penetration rate of echinocandins in the peritoneal fluid are available to date. Additionally, as far as the specific setting of peritoneal dialysis (PD)-associated peritonitis is concerned, it should be mentioned that a recent *in vitro* study showed that the peritoneal dialysis fluids may significantly impair the activities of echinocandins against *C. albicans*, as suggested by the fact that fungicidal activity was achieved only at very high concentration of 128 × MIC [42]. Therefore, in case of *Candida* peritonitis it would be more prudent nowadays to use azoles antifungals which were shown to achieve therapeutically effective levels in the peritoneal fluid, such as fluconazole [43] or voriconazole [44].

Candida endocarditis

Candida is a quite rare cause of infective endocarditis [45]. Combination therapy with liposomal amphotericin B plus flucytosine is currently recommended for the treatment of *Candida* endocarditis [5]. However, it is worth noting that some experimental data showed that the addition of an echinocandin (micafungin) to the combination of liposomal amphotericin B plus flucytosine may be even more fungicidal against simulated *C. albicans* endocardial vegetations than the combination of liposomal amphotericin B plus flucytosine [46]. This support the idea that a combination therapy with three antifungal agents characterized by different mechanisms of action might improve current treatment of *Candida* endocarditis, which is a high-morbidity and -mortality disease.

Candida endophthalmitis

Candida endophthalmitis is a relatively frequent complication of candidemia [47,48]. Low penetration rate after systemic administration of the echinocandins were documented in the ocular compartment, because the eye is a protected compartment [48,49]. Gauthier *et al.* first documented undetectable caspofungin levels after 9 days of systemic therapy in the vitreous of a patient with *C. albicans* endophthalmitis, which were associated with treatment failure [50]. Likewise, very recently it was shown that micafungin levels were very low in the vitreous and aqueous of seven patients with fungal disease who received intravenous injections of 150–300 mg (mean ± SD: 0.08 ± 0.12 mg/l and 0.10 ± 0.07 mg/l, in aqueous and vitreous, respectively) [51].

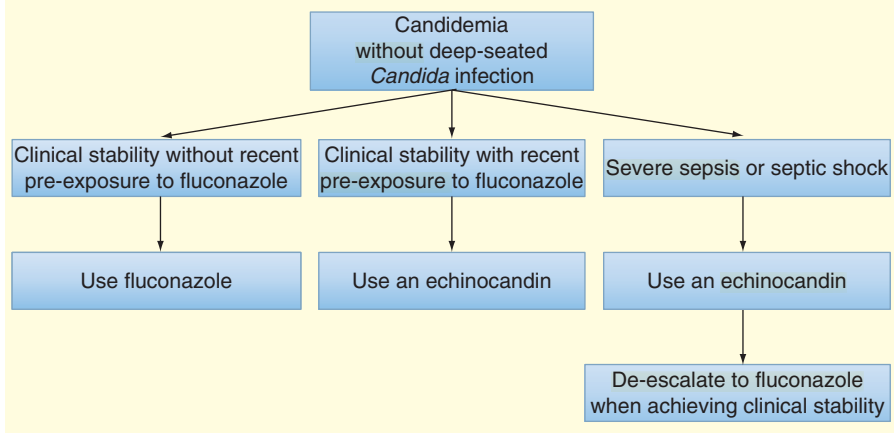

Figure 1. Proposed algorithm for wise use of echinocandins in non-neutropenic patients with candidemia and without concomitant deep-seated *Candida* infection.

In agreement with these findings, clinicians should be aware that echinocandin monotherapy must be avoided whenever *Candida* endophthalmitis is documented or strongly suspected [48]. As far as the risk of ocular candidiasis is concerned, it could be helpful to take care of a recent retrospective study showing that the two most significant risk factors for ocular candidiasis among 204 patients with candidemia (50 of whom with concomitant ocular candidiasis) were a very high serum level of beta-D-glucan (OR: 9.99; 95% CI: 2.60–21.3) and the presence of *C. albicans* as causative pathogen (OR: 3.58; 95% CI: 1.11–12.2) [47].

As a general rule, *Candida* endophthalmitis may benefit by the treatment with a systemic antifungal agent with high penetration in the ocular compartment, as fluconazole [52], voriconazole [53,54] or liposomal amphotericin B [55].

As far as voriconazole ocular diffusion is concerned, achievement of therapeutically effective concentrations in non-inflamed human eye was first documented in 14 patients who underwent elective vitrectomy surgery after oral administration of two 400-mg doses taken 12 h apart before surgery. The percentages of plasma voriconazole concentration in the vitreous and aqueous 3 h after the second voriconazole dose were 38.1 and 53.0%, with absolute mean values in the range of therapeutic concentrations (0.81 and 1.13 mg/l, respectively) [53].

Further data come from a recent case of a patient treated with standard dosages of voriconazole and caspofungin because of a fungal endophthalmitis [56]. Whereas voriconazole achieved therapeutically effective concentrations in the aqueous, with high penetration rate (aqueous vs plasma concentrations 3.47 vs 7.45 mg/l; 46.6%), caspofungin diffused only minimally in that compartment (aqueous vs plasma concentrations 0.28 vs 4.70 mg/l; 6.0%) [56].

As far as amphotericin B ocular penetration is concerned, evidence from an experimental rabbit model suggests that liposomal amphotericin B should be the most valuable amphotericin B formulation for systemic treatment of ocular candidiasis [55]. Notably, amphotericin B concentrations in the vitreous and in the aqueous after 7 days of treatment were higher with 5 mg/kg/day of liposomal amphotericin B (0.47 ± 0.21 and 0.73 ± 0.43 μg/ml) than after 5 mg/kg/day of amphotericin B lipid complex (0.27 ± 0.18 and 0.03 ± 0.02 μg/ml) or with 1 mg/kg/day of amphotericin B desoxycholate (0.16 ± 0.04 and 0.13 ± 0.06 μg/ml).

Candida pyelonephritis

Albeit rare, *Candida* pyelonephritis may be caused by two pathogenetic mechanisms:

- primary candidemia and hematogenous spread to the kidney [57];
- acute pyelonephritis with secondary candidemia, especially in patients affected by diabetes mellitus type 2 [58], obstructive uropathy or in critically ill patients with indwelling urinary catheter.

In all of these cases, first-line antifungal treatment is represented by fluconazole or amphotericin B deoxycholate [4]. However, in case of severe sepsis or of septic shock, the aforementioned drugs could prove to be suboptimal or even dangerous. Fluconazole is not fungicidal and amphotericin B deoxycholate can worsen acute renal injury due to sepsis-induced alteration or renal perfusion. Although lipid formulations of amphotericin B may be less nephrotoxic, they should not be considered as a first choice in this context because of presumed low concentrations of the drug in renal tissue [4]. However, it's worth noting that liposomal amphotericin B was shown to have a urinary clearance, in terms of unbound amphotericin B, similar to that of amphotericin B deoxycholate [59], this suggesting a theoretical potential role for that lipid formulation in this setting.

A valuable choice in presence of *Candida* pyelonephritis associated with candidemia in patients with severe sepsis or with septic shock could be the combination therapy of

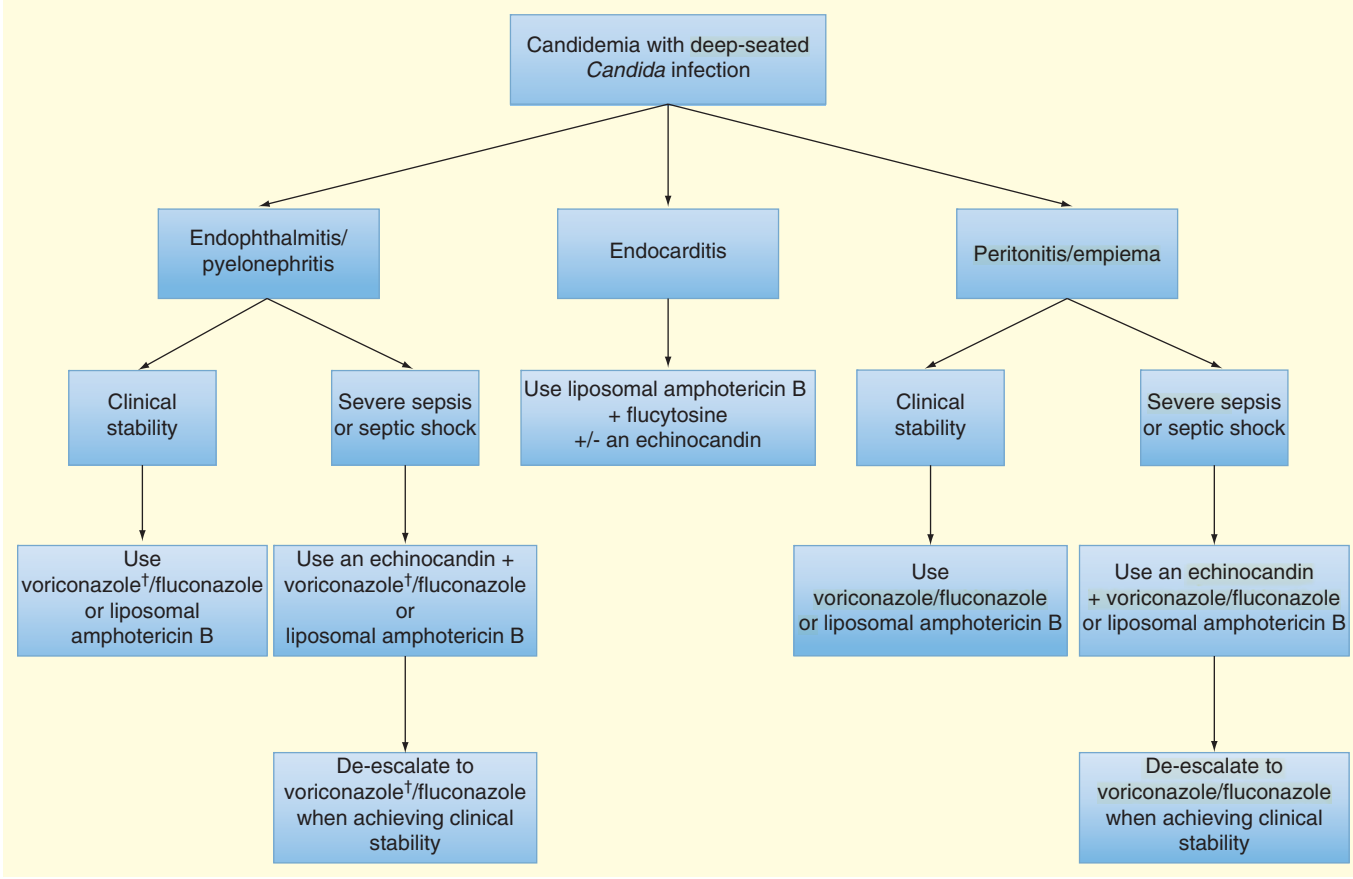

Figure 2. Proposed algorithm for wise use of echinocandins in non-neutropenic patients with candidemia and with concomitant deep-seated *Candida* infection.
†Voriconazole only for endophthalmitis.

fluconazole with an echinocandin, since echinocandins, although unable to reach adequate concentrations in urine, could be useful to hasten candidemia 'clearance' and to reduce sepsis-induced cytokine storm.

Expert commentary

As echinocandin use is greatly increasing nowadays, it's expected that in the next years the incidence of echinocandin resistance in *Candida* spp. could represent a therapeutic challenge to deal with [60]. Echinocandin resistance is usually due to the acquisition of FKS mutations with amino acid substitutions, which confer reduced glucan synthase sensitivity, elevated MICs and are associated with clinical failure [61]. *In vitro* susceptibility testing of the echinocandins using CLSI and EUCAST methods can be used to predict the presence of clinically significant FKS gene alterations among *Candida* strains [62,63].

Implementation of strategies for preserving echinocandin efficacy against *Candida* over time is urgently needed.

From the aforementioned analysis, it may be summarized that treatment with an echinocandin should be advantageous especially in septic critically ill patients with candidemia. Conversely, echinocandin monotherapy should probably be avoided in presence of deep-seated *Candida* infections, for which voriconazole or liposomal amphotericin B may represent valuable alternative agents or add-on therapy.

Accordingly, two valuable algorithms for wise use of echinocandins in non-neutropenic patients with candidemia could be proposed, by taking into account either the patient's clinical status or the presence or absence of deep-seated *Candida* infections (Figures 1 & 2). Early administration of an echinocandin should be preferred for the treatment of candidemia in critically ill patients with severe sepsis or with septic shock, whereas fluconazole could continue to be used in clinically stable patients with no history of recent fluconazole-exposure. In presence of deep-seated *Candida* infections, voriconazole or liposomal amphotericin B may be valuable alternatives or add-on therapies. Additionally, de-escalation therapy from an echinocandin to fluconazole should be applied in septic critically ill patients as soon as clinical stability has been achieved.

Five-year view

In my opinion, the use of echinocandins is expected to increase significantly in the near future, as they have been included in several guidelines for the treatment of *Candida* diseases, for

example, ESCMID [5] and IDSA [4]. Considering the recent report of the appearance of non-*albicans* strains of *Candida* with echinocandin resistance, there is an urgent need for rationalizing echinocandin use in clinical practice. In future, research-specific attention should be paid to selected subpopulation groups, such as critically ill patients with severe sepsis or with septic shock.

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Key issues

- The pharmacodynamic and pharmacokinetic properties support the primary role of the echinocandins in the treatment of *Candida* infections in critically ill patient with severe sepsis or with septic shock.
- Concerns on echinocandin monotherapy exist when in presence of deep-seated *Candida* infections.
- In these cases, voriconazole or liposomal amphotericin B may be valuable alternatives or add-on therapies.
- De-escalation from an echinocandin to fluconazole should be applied in septic critically ill patients when achieving clinical stability.

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