Optimizing Antimicrobial Therapy of Sepsis and Septic Shock

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Fungal Sepsis: Optimizing Antifungal Therapy in the Critical Care Setting

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Invasive fungal infections (IFI) and fungal sepsis in the intensive care unit (ICU) are increasing and are associated with considerable morbidity and mortality. In this setting, IFI are predominantly caused by Candida species. Currently, candidemia represents the fourth most common health care–associated blood stream infection.1–3

With increasingly immunocompromised patient populations, other fungal species such as Aspergillus species, Pneumocystis jiroveci, Cryptococcus, Zygomycetes, Fusarium species, and Scedosporium species have emerged.4–9 However, this review focuses on invasive candidiasis (IC).

Multiple retrospective studies have examined the crude mortality in patients with candidemia and identified rates ranging from 46% to 75%.3 In many instances, this is partly caused by severe underlying comorbidities. Carefully matched, retrospective cohort studies have been undertaken to estimate mortality attributable to candidemia and report rates ranging from 10% to 49%.10–15 Resource use associated with this infection is also significant. Estimates from numerous studies suggest the added hospital cost is as much as $40,000 per case.10–12,16–20 Overall attributable costs are difficult to calculate with precision, but have been estimated to be close to 1 billion dollars in the United States annually.21

Keywords
• Invasive candidiasis • Pharmacokinetics-pharmacodynamics
• Therapy • Source control

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Understanding the management factors that affect outcome in this disease state is thus increasingly important for the critical care physician. The care strategies of demonstrated relevance include prompt suspicion of IC, rapid evaluation, diagnosis and initiation of antimicrobial therapy. In addition, the optimal agent to target these pathogens and the proper dosing regimen must be chosen, and source control should be considered. These care themes are similar to those of demonstrated importance for bacterial sepsis, yet many features are unique to IC. These issues are examined in this review.

EPIDEMIOLOGY

The incidence and epidemiology of IC in the ICU has undergone considerable change in the past 3 decades. This evolution has had a substantial effect on the therapeutic target and thus empirical treatment of IC in the ICU. The incidence of *Candida* blood stream infection (BSI) rose sharply in the 1980s with a more than 5-fold increase compared with studies a decade earlier.\(^\text{22}\) This trend continued with a greater than 200% increase from 1979 to 2000.\(^\text{23}\) The shift in the epidemiology of this health care–associated infection has continued in the current decade, with rates now estimated to be between 25 and 30 per 100,000 persons.\(^\text{16,24}\) In addition to an absolute increase in disease incidence, there has also been a change in the species responsible for these infections. At least 17 *Candida* species have been reported to cause IC in humans, but 5 species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*) represent more than 90%. *C. albicans* has historically been the predominant pathogen in IC with rates of 80% or higher in the 1980s.\(^\text{3,25}\) Presently, *C. albicans* accounts for less than 50% of all BSIs caused by the *Candida* genus.\(^\text{3,26–30}\) The predominant non-albicans species in the United States is *C. glabrata*, with an estimated frequency between 20% and 25%.\(^\text{3}\) In contrast, other countries have noted dramatic increases in *C. parapsilosis* and *C. tropicalis*.\(^\text{3,31}\) As *C. glabrata* often exhibits reduced susceptibility to triazoles and *C. parapsilosis* has reduced susceptibility to echinocandins, knowledge of the local epidemiology is imperative for selection of appropriate empirical therapy.

TIME TO THERAPY

The importance of prompt identification of IC through a combination of risk factor analysis and diagnostic assays has been demonstrated to be a key factor affecting sepsis-related mortality.\(^\text{32–41}\) Studies on patients with IC have similarly shown excessive rates of inappropriate initial therapy and even higher mortality than infections caused by bacterial pathogens in the ICU setting.\(^\text{10,14,33,34,42–47}\) One of the earliest studies to examine the effect of appropriate antimicrobial therapy in the ICU observed a 33% lower mortality in patients receiving adequate therapy defined by in vitro antimicrobial susceptibility testing.\(^\text{33}\) Inappropriate treatment was most common for *Enterococcus* spp; however, inadequate coverage for IC was the second most common error and was associated with the highest mortality. Another retrospective cohort study by Kumar and colleagues\(^\text{34}\) demonstrated that administration of adequate antimicrobial therapy within the first hour of documented hypotension was associated with a survival rate of 79.9%, and each 1-hour delay in antimicrobial therapy was linked to a 7.6% per hour decrease in survival. Subgroup analysis identified a significant relationship between hospital survival and duration of time between onset of sepsis and drug therapy for each microbial genus including *Candida* species.

Additional studies investigating the effect of time to initial appropriate therapy have specifically targeted IC. Blot and colleagues\(^\text{42}\) reported 78% mortality in patients with IC when therapy was delayed more than 48 hours from onset of candidemia; in
contrast the mortality was 44% in those who had adequate initial therapy. Another single-center retrospective cohort of 157 consecutive patients with a Candida BSI showed a trend toward improved survival when appropriate antifungal therapy was administered within 12 hours of blood culture collection (mortality 11.1% vs 33.1%; \( P = .169 \)). In multivariate analysis the odds of death was 2-fold higher if adequate therapy was delayed more than 12 hours \( (P = .018) \). Garey and colleagues examined time to antifungal therapy in a multicenter, retrospective cohort of 230 patients with a Candida BSI who were prescribed fluconazole. Mortality was lowest (15.4%) if fluconazole therapy was started on the same day that the culture was performed and increased to 23.7% if fluconazole therapy was started on day 1, 36.4% on day 2, and 41.4% if it was started day 3 \( (P = .0009) \). Multivariate analysis in this study also provided a strong association between delay in therapy and mortality. In a recent publication, Patel and colleagues performed a retrospective review of cases of Candida sepsis (positive blood culture within 72 hours of refractory shock) from a single center from 2003 to 2007. Using classification and regression tree analysis (CART), they found patients who received early, appropriate antifungal therapy (within 15 hours of collecting the first positive blood culture) had improved survival. Another recent publication by Taur and colleagues in a cohort of patients with cancer found similar results. These data strongly support early appropriate antifungal therapy and demonstrate a need for improved disease identification.

**EARLY DIAGNOSTICS**

Two areas of intense investigation designed to improve early IC identification include novel laboratory assays and risk factor–based disease prediction. Unfortunately, IC lacks specific and objective clinical findings. In addition, the gold standard diagnostic test for IC has been isolation of the organism in blood culture, however, blood culture for Candida is insensitive. For example, modern blood culture systems are estimated to detect only 50% to 67% of cases of IC. Furthermore, detection of candidemia by blood culture often takes more than 24 hours. For certain species, such as C glabrata, the time to positive culture can be even longer. In a study by Fernandez and colleagues, the mean time to yeast detection in blood cultures for C albicans was 35.3 ± 18.1 hours, whereas that of C glabrata was 80.0 ± 22.4 hours. Mean time to final identification to species level for C albicans was 85.8 ± 30.9 hours compared with 154 ± 43.8 hours for C glabrata. In this study, the time to appropriate therapy for C albicans isolates was 43.3 ± 27.6 hours compared with 98.1 ± 38.3 hours for C glabrata isolates. Thus, waiting for positive blood culture results and potentially susceptibility testing leads to a significant delay in appropriate therapy and in turn higher mortality.

The relatively slow growth of these organisms in culture systems has led to the development of several non–culture-based diagnostic studies to detect fungal cell wall components, antigens, or nucleic acids secreted into the blood. Approved serologic tests in the United States or Europe include mannan antibody/antigen detection (Platelia) and \( \beta \)-1,3-D-glucan (Glucatell, Fungitell). In Europe, a nucleic acid identification system (SeptiFast) is approved for detection in blood of certain bacterial and fungal pathogens including the 5 most commonly encountered Candida species.

A retrospective study evaluated mannan antigen or mannan antibody detection in the sera of patients with culture proven candidemia. In 36 of 43 (84%) patients with culture proven candidemia at least 1 of the 2 serologic tests was positive. The sensitivities were 40% and 98% and the specificities were 53% and 94% for mannanemia or antibody detection, respectively. These values reached 80% and 93% when the results of both
tests were combined. A follow-up study of patients with candidemia revealed that 33 of 45 (73%) patients had positive serology using the Platelia assay for mannan antigen or antimannan antibodies at least 2 days before having a positive blood culture, with a mean positive serologic test 6 days before positive blood culture. \( \beta-1,3\)-D-Glucan detection has also been evaluated in critically ill patients, with sensitivity and specificity for diagnosis of IC estimated to be 69.9% and 87.1%, respectively. Several nucleic acid detection platforms have been evaluated for detection of IC. For example, McMullan and colleagues prospectively evaluated 3 Taqman-based nested polymerase chain reaction (PCR) assays for the detection of candidemia in critical ill patients. Twenty-three of 157 patients included in the study had proven IC. The estimated clinical sensitivity, specificity, and positive and negative predictive values of the assays in this trial were 90.9%, 100%, 100%, and 99.8%, respectively. Nucleic acid detection in this study identified fungal sepsis as soon as 6 hours within onset of symptoms. SeptiFast, which is able to detect DNA of 20 common bacteria and fungi, may be a helpful adjunct to blood cultures for fastidious organisms and may be advantageous in settings where patients are either already on antibiotics or have been pretreated. An important limitation in evaluating these newer diagnostic tests is the lack a reference gold standard (blood culture) with high specificity and sensitivity. For example, in a meta-analysis of studies using PCR to diagnose IC, the sensitivity progressively decreased as the reference standard went from patients with culture proven candidemia to those with proven/probable IC, and even lower when compared with those with proven, probable, or possible IC. At present, there is significant heterogeneity in assay characteristics including choice of sample, primer, nesting strategy, and nucleic acid extraction. Although promising, there is need for further prospective validation of these diagnostic tools and wider availability, as currently only a few academic centers or reference laboratories have the capability to offer these advanced diagnostic techniques. Until confirmatory results are available from ongoing studies, routine use of these new diagnostic assays will remain investigative. If the empirical trial use of the \( \beta-1,3\)-D-glucan test is shown to be useful, it is reasonable to expect this assay could be adapted for use in most tertiary care centers in the near future.

**EMPIRICAL AND PREEMPTIVE STRATEGIES BASED ON RISK IDENTIFICATION**

The importance of prompt antifungal treatment and lack of sensitivity and timeliness of diagnostic assays has led to the development of empirical and preemptive treatment strategies. The initiation of antifungal treatment in these cases is based on a compilation of host risk factors for IC. Multiple studies have evaluated risk factors for IC. Variables that have been associated with IC include high APACHE II score, exposure to broad spectrum antibiotics, cancer chemotherapy, evidence of mucosal colonization by *Candida* spp, pancreatitis, indwelling vascular catheters (especially central venous catheter [CVC]), administration of total parenteral nutrition, neutropenia, immune suppression therapy, prior surgery (especially gastrointestinal surgery), renal failure or hemodialysis, and prolonged ICU stay (especially in the surgical ICU). These risk factors by themselves impart limited specificity as they are present in many critically ill patients.

Attempts to enhance the predictive value of these variables have involved examining a composite of risk factors. A laboratory marker used in several risk stratification schemes is culture isolation of *Candida* species from multiple nonblood sites. The predictive value of this laboratory marker by itself has been explored by Pittet and colleagues, who examined the value of identifying *Candida* colonization at multiple nonblood sites, termed the *Candida* colonization index (CI).
This index is calculated by adding the number of nonblood sites that are culture positive for the same *Candida* species divided by the total number of sites cultured. In a single-center prospective series the group found an index greater than 0.5 to be predictive of IC in 29 patients with *Candida* colonization in either a surgical or neonatal ICU. The sensitivity and specificity of the CI was 100% and 55%, respectively, using positive blood culture as the reference. This strategy requires daily multisite *Candida* surveillance cultures, which may not be feasible or cost-effective at many centers and results would still be delayed to allow for culture growth. Additional studies have examined the usefulness of multisite colonization in the context of other risk factors. For example, Leon and colleagues\textsuperscript{88} developed a scoring system that could be performed at the bedside termed the *Candida* score. In a large, multisite observational study they examined the incidence of IC among patients in a surgical ICU with sepsis, total parenteral nutrition (TPN) administration, multifocal *Candida* colonization. A point value was assigned to each of 4 risk factors (multifocal colonization 1 point, TPN 1 point, surgery 1 point, and sepsis 2 points). Patients with a score greater than 2.5 were nearly 8 times more likely to have proven IC (risk ratio 7.75; 95% confidence interval 4.74–12.66) than patients with a *Candida* score of 2.5 or less. The strategy was prospectively validated in a larger cohort of 1107 patients in the surgical ICU among whom 57 were diagnosed with candidemia. Patients with a *Candida* score greater than 2.5 had a 6-fold increase in relative risk for developing IC with a sensitivity of 77.6% and specificity of 66.2%.\textsuperscript{89}

Other studies have relied solely on non–laboratory-based risk factors. Ostrosky-Zeichner and colleagues\textsuperscript{90} performed one of the largest studies examining a clinical risk prediction rule for IC. Among 3000 patients from ICUs in the United States and Brazil, a combination of several factors was predictive of IC in patients who had been admitted to the ICU for at least 3 days. The study identified both major and minor risk factors. The 2 major risk factors included receipt of a systemic antibiotic and the presence of a CVC. Minor risk factors included TPN, dialysis, surgery in the preceding week, pancreatitis, and use of steroids or other immunosuppressive agents. Patients meeting both major risk factors and at least 2 minor risk factors constituted the high-risk group. Retrospective analysis identified a rate of invasive candidiasis among patients who fulfilled the criteria of 9.9% versus 2.3% in those who did not meet criteria. The clinical prediction rule was relatively exclusive as the total number of patients who met criteria was only 11% (n = 303) of the total population studied. The calculated sensitivity was only 34%, but specificity was 90%. A follow-up prospective validation study by the same group evaluated a modified clinical prediction rule in a medical ICU.\textsuperscript{91} Patients meeting criteria must have been in the medical ICU for at least 3 days, have both major criteria (a CVC and antibiotic exposure), and have at least 2 minor criteria (which included mechanical ventilation in place of surgery given the study was performed in a medical ICU). Patients meeting these criteria were given fluconazole preemptively. In the year before the implementation of the rule, 9 cases of candidemia developed in the medical ICU, corresponding to a rate of 3.4 cases per 1000 CVC days. In the year of implementation, only 2 cases of candidemia were identified, a drop in the rate of *Candida* bloodstream infection to 0.8 cases per 1000 CVC days.

Further validation of risk assessment tools and assessment of the value of antifungal prophylaxis and preemptive therapy are necessary before clinical adoption of this practice. Currently, there is an ongoing multisite, randomized, double-blind, placebo-controlled trial sponsored by the Mycoses Study Group examining this risk stratification scoring system and caspofungin prophylaxis followed by preemptive therapy for IC in high-risk adults in the critical care setting.\textsuperscript{92} The results may provide valuable insight into both risk stratification schemes and prophylaxis in the ICU.
ANTIFUNGAL DRUG CLASSES AND MECHANISM OF ACTION

Once either a definitive diagnosis occurs or risk factors trigger the initiation of therapy, the next step in management is the choice of the optimal antifungal agent and dosing regimen. Differences in the mechanism of action, spectrum of activity, pharmacokinetics, and toxicity affect this decision for a variety of clinical situations. Currently, 3 classes of antifungal drugs, a total of 8 drugs, are approved by the US Food and Drug Administration (FDA) for IC. The first class of antifungals that became available for treatment of IC is the polyene group, which includes amphotericin B deoxycholate and its 3 lipid formulations (liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B cholesteryl sulfate complex). Of the 4, only amphotericin B cholesteryl sulfate does not carry an FDA indication for candidemia. The lipid formulations have been a major advance in therapeutics, providing less nephrotoxicity than that observed with conventional deoxycholate amphotericin B. All of the formulations exert their cidal effect by binding to ergosterol in the fungal cell membrane leading to depolarization, increased permeability, and ultimately cell death.93 The second class of antifungal compounds is the triazoles; FDA-approved agents for IC include fluconazole and voriconazole. These drugs target fungal cell membrane ergosterol synthesis, the major cell membrane component, by inhibition of the fungal cytochrome P-450–dependent enzyme lanosterol 14-α-demethylase. This mechanism of action is generally considered fungistatic against Candida species.93 The most recently developed group of antifungals is the echinocandin class, which includes caspofungin, micafungin, and anidulafungin. All 3 are FDA approved for candidemia and are cidal against Candida species.93–95 The mechanism of action for this class is via inhibition of β-1,3-glucan synthase, an enzyme responsible for production of the major cell wall component β-1,3-D-glucan.

SPECTRUM OF ACTIVITY

Amphotericin B deoxycholate and its lipid congeners are potent against most Candida species. Among the species that are less susceptible to this drug, C glabrata and C krusei have MIC90s (minimum inhibitory concentration required to inhibit 90% of organisms) of 4 and 8 μg/mL, respectively, compared with an MIC90 of 1 μg/mL for C albicans.3 Although the MIC for C lusitaneae is often comparable with C albicans on initial susceptibility testing, this species is notorious for development of resistance while on therapy with amphotericin B.

Fluconazole and voriconazole are also active against most Candida species including C albicans, C parapsilosis, and C tropicalis. Reduced activity is a concern for a few commonly identified species, specifically C glabrata and C krusei. C krusei is inherently resistant to fluconazole and therefore is not effective. Fluconazole resistance in C glabrata varies by geographic location with rates of 14% to 23%, with an additional 5% susceptible only to increased doses of fluconazole (susceptible dose-dependent).3,96 Reduced C glabrata susceptibility to fluconazole is in general predictive of activity for the entire triazole class including voriconazole. However, a small subset of fluconazole resistant C glabrata isolates, approximately 17%, do remain susceptible to voriconazole.97 A unique spectrum for voriconazole includes C krusei.

The echinocandins offer a broad spectrum that includes activity against C albicans, C glabrata, C tropicalis, and C krusei. Both C guilliermondii and C parapsilosis have reduced susceptibility to the echinocandin class. Clinical trials have not fully examined the importance of the decreased susceptibility of these 2 species, although case reports of treatment failure continue to accumulate.98–103
OPTIMAL DRUG CHOICE

The optimal drug choice for IC has been evaluated in numerous clinical studies and several consensus guidelines have been published. Amphotericin B had long been considered the only treatment of IC before the approval of fluconazole. In 1994, Rex and colleagues published the first comparative trial examining antifungal therapy (fluconazole vs amphotericin B) in non-neutropenic patients with candidemia. Similar successful clinical outcomes were noted in both groups (fluconazole 70% vs amphotericin B 79%). Significant adverse events (AE) were more common in the amphotericin B group including electrolyte imbalance and renal insufficiency. A study by Kullberg and colleagues demonstrated similar successful clinical outcomes in patients with IC or candidemia treated with voriconazole compared with amphotericin B with step down to fluconazole. Significantly fewer serious AE attributable to the antifungal drug occurred in the voriconazole group versus amphotericin B. Mora-Duarte and colleagues published the first comparative trial of an echinocandin and amphotericin B in 2002. This trial compared outcomes in patients with blood culture proven candidemia or IC, defined as having a positive culture from a sterile site, who received caspofungin or amphotericin B. Successful outcomes, although not significantly different, were noted in 73.4% of patients receiving caspofungin and 61.7% in those who received amphotericin B. This trial also highlighted the generally low incidence of AE and excellent tolerability for the echinocandin class. Caspofungin had significantly less clinical or laboratory AE, with only 2.6% of patients in this arm discontinuing therapy. This is in contrast to amphotericin B, which was associated with clinical AE (nausea, vomiting, chills, fever) as well as laboratory AE (electrolyte imbalances, renal insufficiency) resulting in nearly a 25% rate of drug discontinuation. In recent years, micafungin and anidulafungin have also been subjected to study in randomized controlled trials (RCTs). In a study by Kuse and colleagues, micafungin was as effective and caused fewer AE than liposomal amphotericin B as first-line treatment of candidemia and invasive candidiasis. Most recently, Reboli and colleagues examined anidulafungin versus fluconazole, with anidulafungin showing superiority over fluconazole. In this study, successful outcome was noted in 75.6% versus 60.2%, respectively, in patients with candidemia or IC. AEs in this trial were similar between anidulafungin and fluconazole. The sum of these studies has shown low toxicity (especially compared with amphotericin B) and equivalent or improved outcome data when echinocandins are compared with azoles or amphotericin B.

Recently, a patient-level meta-analysis of RCTs for treatment of IC was performed, drawing data from 7 trials conducted from 1994 to 2007 and including more than 1800 patients. The use of an echinocandin rather than another antifungal agent was associated with decreased mortality.

The Infectious Diseases Society of America (IDSA) has recently published revised recommendations for the treatment of IC. In the current guidelines, first-line options include caspofungin, anidulafungin, micafungin, or fluconazole. The guideline favors an echinocandin for moderate to severe IC or any patient with previous azole exposure, with the exception of C parapsilosis for which fluconazole is suggested. Transition from an echinocandin to fluconazole is suggested when an isolate that is likely to be susceptible to fluconazole (eg, C albicans, C tropicalis, C parapsilosis) is identified and patients have clinically stabilized. Voriconazole therapy may be appropriate for C krusei and C glabrata in place of fluconazole for stable patients with laboratory-demonstrated susceptibility to this agent. Amphotericin B and its lipid formulations remain important antifungal agents for serious fungal infections including IC despite its known toxicities. With the advent of less toxic but equally effective therapy,
amphotericin B is now reserved for patients who are intolerant to echinocandins, those not responding to echinocandins, or special circumstances such as meningitis with Candida species.

**TOXICOLOGY**

Although amphotericin B deoxycholate exhibits the widest spectrum of activity, administration is associated with limiting adverse effects. Up to 50% of patients experience infusion-related toxicity, which includes nausea, vomiting, fever, chills, rigors, myalgias, and rarely bronchospasm and hypoxia. Electrolyte imbalance (hypokalemia, hypomagnesemia) caused by distal renal tubular toxicity and renal insufficiency secondary to vasoconstriction have been reported in up to 80% of patients. Preinfusion administration of an antipyretic and antihistamine agent may reduce infusion effects and hydration with normal saline provides some mitigation of the renal insufficiency. Some investigators have suggested that administration of deoxycholate amphotericin B by a continuous infusion may decrease nephrotoxicity, but comparative efficacy has not been studied prospectively or with a large enough sample in a retrospective manner. Most of the data are from preemptive therapy in high-risk hematology patients with febrile neutropenia. Thus, further studies would need to examine this dosing strategy in a controlled fashion for IC before any recommendations can be made for this approach. The most affective reduction in polyene toxicity is with use of a lipid formulation, which is associated with 10- to 20-fold fewer febrile reactions and renal insufficiency.

The triazoles and echinocandins are in general well tolerated with few significant adverse effects. The most common complication of triazole use is that associated with drug interactions caused by P-450 inhibition or induction. The echinocandins are associated with very few and mostly minor drug interactions.

**PK CONSIDERATIONS**

Consideration of infection site drug concentrations can be important when choosing the optimal antifungal. There are certain tissues for which there are pharmacokinetic differences among the antifungal agents. For most tissue sites, serum concentrations correlate closely with interstitial tissue concentrations where most fungal pathogens reside during infection. However, there are certain tissue sites for which there can be discrepancies, including the central nervous system (CNS), eye, urine, and the epithelial lining fluid of the lung. The CNS, eye, and urine body sites are tissue sites of importance for a subset of patients with IC. Amphotericin B and its lipid formulations have differing tissue pharmacokinetics that are largely dependent on the carrier molecule to which they are complexed. For example, liposomal amphotericin B is a small, unilamellar particle that exhibits high serum and CNS concentrations relative to the other amphotericin B preparations. A few investigations have explored the effect/affect of these PK differences on outcomes, with a CNS candidiasis animal model in favor of the liposomal amphotericin B formulation. This lipid formation also accumulates in the vitreal fluid, which may be attractive for endophthalmitis therapy.

Fluconazole penetrates into nearly all tissue sites including CSF, vitreous fluid, and urine, and is therefore a valuable drug to treat sequestered sites of infection against susceptible Candida species. Voriconazole also has wide tissue distribution including the CSF and vitreal fluid, but is not excreted into urine and would not be expected to be effective for Candida cystitis.
The echinocandins are large lipopeptide antifungal agents available only as intravenous formulations because of their chemical structure and size, which precludes adequate oral absorption. These physiochemical characteristics also affect the distribution of these compounds, which is notably low or undetectable in urine, CSF, and vitreous fluid.\textsuperscript{95,125,126}

**OPTIMAL DOSE AND REGIMEN**

Treatment success following early initiation and correct drug choice will be limited if the optimal dose and dosing schedule are not considered. Numerous reports have documented the association between inadequate dosing of antifungals in patients with IC and increased length of hospital stay, health care costs, morbidity, and mortality.\textsuperscript{10,14,20,33,42–47,127} Pharmacodynamic (PD) analyses have been crucial in developing optimal anti-infective dosing strategies. These approaches simply consider the effect of pharmacokinetics (PK) of a drug relative to the MIC of the organism on therapeutic efficacy.\textsuperscript{128} Pharmacodynamic application has revolutionized treatment of bacterial infections in the ICU setting.\textsuperscript{128,129} More recently, similar study results have become available for antifungal agents in this setting.\textsuperscript{93,130}

Three PD indices have been linked to therapeutic efficacy. Each of these drug exposures indices represents a measure of drug PK relative to the MIC of the infecting organism. The indices include the peak drug concentration indexed to the MIC \((C_{\text{max}}/\text{MIC})\), the area under the drug concentration curve in relation to the MIC \((\text{AUC}/\text{MIC})\), and the time (expressed as a percentage of the dosing interval) that the drug concentrations exceed the MIC \((%T>\text{MIC})\). Determining which of the 3 PD indices is predictive of efficacy for an antimicrobial agent provides a framework for dosing regimen design. For example, dosing of concentration-dependent antimicrobials is optimal when large doses are administered infrequently. The concentration-dependent indices, \(C_{\text{max}}/\text{MIC}\) and \(\text{AUC}/\text{MIC}\), are the PD indices associated with treatment efficacy for these compounds. Conversely, efficacy for antimicrobials that exhibit time-dependent activity is greatest when smaller doses are given frequently. In this scenario, maximal antimicrobial effects are observed at concentrations near the MIC. The optimal regimen design in this case would aim to keep drug concentrations higher than the organism’s MIC for a longer period of time and the predictive index for these antimicrobials is the \(%T>\text{MIC}\).

A PD study also has the ability to define the amount of antimicrobial relative to the MIC that is needed for efficacy. This drug exposure indexed to the MIC is termed the pharmacodynamic target. For example, if \(%T>\text{MIC}\) is the PD index linked to efficacy, the PD target is how much time concentrations need to exceed the MIC for optimal efficacy. These investigations have been undertaken for each of the antifungal drugs.

**Amphotericin B and the Lipid Formulations**

Despite the common dose-limiting toxicities, amphotericin B remains an important therapeutic option for life-threatening fungal infections, especially in resource-limited areas. In vitro and in vivo PD studies have observed increased killing of *Candida* species as the concentration of amphotericin B is escalated multiple times higher than the MIC.\textsuperscript{120,131–133} These models have also shown that growth inhibition after amphotericin B exposure continues for long periods of time. This period of postexposure effect is called the postantifungal effect (PAFE).\textsuperscript{131,133,134} Prolonged PAFEs should allow for wider spacing of the dosing intervals. These PD characteristics support once daily administration of maximally tolerated doses. The concentration-dependent PD index \(C_{\text{max}}/\text{MIC}\) has been most closely linked to efficacy in these
infection models. The concentration relative to the MIC associated with maximal efficacy in experimental models is a C\text{max}/MIC of 2 to 4.\textsuperscript{120,131} Pharmacodynamic analyses have also been undertaken with the 3 lipid formulations of amphotericin B.\textsuperscript{120–123} These investigations have demonstrated similar pharmacodynamic characteristics; however, for lipid preparations the C\text{max}/MIC target needed for efficacy is approximately 5 times larger than for amphotericin B.\textsuperscript{120} There is a single, small clinical PD report with liposomal amphotericin B in a pediatric population.\textsuperscript{135} Among 39 patients, those with liposomal amphotericin B C\text{max}/MIC >40 were more likely to achieve a complete or partial response. This clinical target is similar to that identified in animal model studies. No other clinical investigations with the polyenes have provided data that would allow PD analysis.

**Triazoles**

Extensive PD studies have been undertaken with fluconazole and voriconazole.\textsuperscript{133,136–139} Observations from these investigations demonstrated time-dependent antifungal activity that was optimal at concentrations 1 to 2 times the MIC. In addition, in vivo studies have revealed prolonged periods of growth suppression after triazole concentrations decrease to less than the MIC (long PAFE).\textsuperscript{139–141} These characteristics are consistent with drugs for which the AUC/MIC index is most closely linked with efficacy. In vivo animal studies against a large number of *Candida* strains with widely varying MICs (more than 2000-fold) show that the 24-hour AUC/MIC target associated with efficacy (50% maximal effect) for triazoles occurs at a value near 25 when free drug (non–protein bound) levels are considered.\textsuperscript{139–141} Simplicistically, this value is the average concentration at the MIC for a 24-hour dosing period (1 times the MIC times 24 hours equals a 24-hour AUC/MIC of 24).

Substantial clinical data are available for pharmacodynamic target analyses for fluconazole in the treatment of *Candida* infections.\textsuperscript{142–148} The earliest and largest of these datasets included more than 1000 patients with oropharyngeal candidiasis.\textsuperscript{146} Analysis of these trial data found that treatment efficacy was maximal with fluconazole exposures relative to the MIC of the infecting *Candida* species near a 24-hour AUC/MIC value of 25. When the fluconazole AUC/MIC exceeded 25, clinical success was noted in 91% to 100% of patients. However, when AUC/MIC was less than 25, clinical failure was noted in 27% to 35% of patients. A more contemporary analysis in mucosal candidiasis corroborated the earlier findings, with clinical efficacy of 92% with an AUC/MIC greater than 25 and only 9% with values less than 25.\textsuperscript{147} Similar data are available for IC.\textsuperscript{142,143,145,147,148} For example, Baddley and colleagues\textsuperscript{142} examined the relationship between the fluconazole 24-hour AUC/MIC and mortality in patients with IC. Maximal survival was associated with an AUC/MIC of 25.

Calculating the AUC/MIC magnitude for fluconazole is relatively straightforward as the AUC is essentially equal to the daily dose (400 mg daily dose is approximately an AUC of 400). One can then use the PD target information to define the highest MIC for which a given dosing regimen would be expected to be adequate. For example, with a fluconazole dose of 400 mg once daily for an infection in which the MIC is 32, the AUC/MIC would be less than 25 and failure can be expected. Surveillance MIC data can then be used to estimate if a drug and dosing regimen would achieve the PD target for most organisms in the community. *C albicans* has the lowest wild-type MICs with 98.1% having an MIC of 0.5 \(\mu g/mL\) or less.\textsuperscript{149} *C parapsilosis*, *C tropicalis*, and *C lusitaneae* also have low MICs of 2 \(\mu g/mL\) or less (93%, 98% and 96%, respectively).\textsuperscript{149} The wild-type MICs are significantly higher for *C guilliermondii* (8–16 \(\mu g/mL\)), *C glabrata* (32 \(\mu g/mL\)), and *C krusei* (64–128 \(\mu g/mL\)).\textsuperscript{149} Therefore, for these MIC distributions, a fluconazole regimen of 400 mg per day would be an
effective empirical option for most patients infected with *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, but not *C. glabrata* or *C. krusei*.

Similar data are available for the triazole, voriconazole. The largest dataset includes more than 400 patients from 6 phase III clinical trials.\textsuperscript{150} Analysis of this dataset demonstrated a strong relationship between AUC/MIC and outcome. Therapeutic success was observed in approximately 80% of patients with a 24-hour AUC/MIC greater than 25, whereas when the AUC/MIC was less than 25, clinical failure was noted in 45% of patients. Many of these studies have also highlighted the variable PK of voriconazole, and the usefulness of therapeutic drug monitoring has been suggested in the setting of invasive aspergillosis.\textsuperscript{151–154} Treatment success in these retrospective analyses has been associated with serum trough concentrations of 1 to 2 mg/mL. If the free drug AUC associated with these trough concentrations and the MIC for voriconazole against *Aspergillus* are considered, the 24-hour AUC/MIC value would be near 25. Although not well studied in IC, the PK/PD congruency in target AUC/MIC between *Aspergillus* and *Candida* would suggest target trough concentrations should be at least 1 to 2 mg/mL for IC and concentration monitoring might be useful in the critical care setting.\textsuperscript{155}

**Echinocandins**

PK/PD studies with the echinocandin class of antifungals demonstrate concentration-dependent activity with a prolonged PAFE similar to that observed with amphotericin B.\textsuperscript{156–163} The concentration-dependent indices, C\textsubscript{max}/MIC and AUC/MIC, are both closely linked to efficacy and support administration of large infrequent doses. Preclinical and clinical PK/PD investigations have sought to identify the amount of echinocandin indexed to MIC that is needed for optimal therapy. In addition to examining the effect of MIC variability, a unique feature of these studies has included examination of the potential effect of *Candida* species on the PD target.\textsuperscript{164,165} The results of these studies demonstrated the amount of echinocandin relative to the MIC needed for efficacy was higher for *C. albicans* than for *C. glabrata* or *C. parapsilosis*.\textsuperscript{165} The free drug AUC/MIC target was much less for *C. parapsilosis* and *C. glabrata* at approximately 5 to 7, whereas for *C. albicans* the target AUC/MIC was approximately 10 to 20. Identification of species variability in the PD target is not a new paradigm. For example, studies with fluoroquinolone antibacterials identified an AUC/MIC target for *Streptococcus pneumoniae* of 25, whereas for gram-negative bacteria the value was near 100.\textsuperscript{166} Clinical trial data with all 3 echinocandins have shown that the available drugs can be used successfully to treat *C. parapsilosis* infections with increased MICs.\textsuperscript{164,167} For example, in one report 5 of 6 (83%) infections caused by *C. parapsilosis* for which the MIC was 4 μg/mL were treated successfully with anidulafungin, which would support the finding that the PD target may be much lower for this species.\textsuperscript{167} Robust PD analysis of the echinocandin class using clinical patient data is limited. One dataset has been evaluated in this manner thus far. Analysis of 2 phase III trials with micafungin for candidemia or invasive candidiasis identified similar species-specific results.\textsuperscript{168} Results from this investigation found a free drug AUC/MIC target of greater than 7.5 was associated with favorable outcomes for all *Candida* species except *C. parapsilosis*, for which a free drug AUC/MIC magnitude predictive of favorable outcome was near 1. Recognition of differences in species-specific PD targets have recently been incorporated into the Clinical Laboratory and Standards Institute antifungal susceptibility breakpoint guidelines for each of the approved echinocandins.\textsuperscript{169} The pharmacokinetics of the present echinocandin dosing regimens would be expected to produce AUC/MIC values exceeding these pharmacodynamic target goals for most *Candida* isolates. Thus, although
dose adjustments should not be needed at present, if surveillance susceptibility testing identifies the emergence of less susceptible isolates, safety studies with each of the available echinocandin compounds can be escalated without toxicity.

COMBINATION THERAPY

Combination therapy is a frequently used strategy for difficult to treat infectious diseases. However, combination antifungal therapy has not been well studied for IC. Consensus guidelines do suggest a combination of amphotericin B and flucytosine for some infection types such as Candida meningitis, endophthalmitis, and endocarditis. A single, randomized clinical trial examined high-dose fluconazole versus standard fluconazole dosing and amphotericin B in patients with candidemia. For several outcomes there was a trend in favor of the combination; however, the 2 groups had significant differences in baseline APACHE II score favoring the combination arm. Robust PK/PD analysis of combination therapy is lacking and would provide useful guidance in this area.

DURATION

There are no experimental or clinical trials designed to define the optimal duration of therapy for IC. Guidance is based on expert consensus publications. The IDSA guideline for invasive candidiasis recommends a 2-week treatment duration following clearance of Candida from the bloodstream and resolution of symptoms attributable to candidemia. Longer durations are recommended for persistent candidemia and for metastatic infection involving other sites (ie, CNS, bone, endocarditis, joint/prosthetic joint infection).

DEESCALATION

Deescalation or step down therapy from intravenous echinocandin or polyene to oral therapy is a common strategy but has not been formally studied. In most of the randomized trials, patients treated with either an echinocandin or polyene were allowed to step down to oral therapy (fluconazole or voriconazole) after receiving at least 10 days of intravenous therapy. In 1 study, patients were allowed to step down to oral fluconazole therapy in as few as 3 to 7 days after intravenous therapy with amphotericin. However, the timing of step down has not been specifically analyzed in these investigations. Treatment guidelines recommend step down to fluconazole for patients who have improved clinically after initial therapy with an echinocandin or amphotericin B and who are infected with an organism that is likely to be susceptible to fluconazole (eg, C albicans, C parapsilosis, and C tropicalis) or if there is documented susceptibility based on laboratory MIC testing. It is possible that even shorter durations of parenteral therapy may be effective; however, future studies will be needed to appropriately address this important question.

SOURCE CONTROL

Source control of infectious foci is an additional measure commonly used for IC. The rationale for source control includes removal of persistent infection and decreasing the infectious burden at pharmacologically protected sites. There are 2 common IC syndromes for which a source control strategy has been useful. The first is extirpation of biofilm infections because of the high level of drug resistance associated with this form of growth. This typically occurs in the setting of indwelling medical devices such as vascular and urinary catheters. Venous catheter infection and IC guidelines,
including the current IDSA guidelines, recommend removal of any intravascular catheter that is positive for a fungal pathogen (ie, *Candida*) based on evidence from large retrospective and observational studies.\textsuperscript{110,170–178} A few studies have questioned these recommendations, failing to find a significant mortality benefit with prompt removal of the line and advising that removal and placement of a new device does not come without risk and cost.\textsuperscript{179–183} For example, a recent publication by Nucci and colleagues\textsuperscript{183} examined the effect of early (within 24 or 48 hours) CVC removal in subgroup analysis of data pooled from 2 phase III, double-blind, multicenter RCTs of therapy for candidemia. A total of 1109 patients were included in the 2 groups. After inclusion/exclusion criteria, 842 patients were included in the analysis. The investigators found no clinical difference in microbiologic outcomes or mortality in the patient group that had the CVC removed within 48 hours versus those that had it retained for the first 48 hours. These data are in contrast to a study published in the same year using the same dataset. Horn and colleagues\textsuperscript{178} used the same 2 phase III datasets and found that catheter retention was associated with poorer outcomes than patients who had it removed. The differences in these 2 retrospective studies using the same datasets are to the result of different methodological processes, including the definitions used, inclusion/exclusion criteria, and statistical analysis. The largest study to date examining line retention and outcome is a meta-analysis of RCTs for treatment of invasive candidiasis, drawing data from 7 trials from 1994 to 2007 and including more than 1800 patients.\textsuperscript{111} Removal of a CVC in patients with candidemia was associated with a 13% increase in survival.

A second site for which source control can be critical is infection of the vitreous. Endophthalmitis is a not uncommon complication in patients with candidemia, with an incidence ranging from 3% to 28% in prospective studies, and carries significant morbidity.\textsuperscript{126} The accumulation of therapeutic agents in the vitreous is limited for many compounds and there is variability among the available antifungal agents. Therefore, the current guidelines suggest ophthalmologic examination for every patient with candidemia.\textsuperscript{110} Recommended antifungal therapies include amphotericin B, fluconazole, or voriconazole depending on the susceptibility of the isolate. Although not studied in randomized comparative trials, vitrectomy is considered an important adjunct to antifungal therapy and can be a sight-saving procedure.\textsuperscript{184}

**PROPHYLAXIS AND PREEMPTIVE THERAPY**

Although it is outside the scope of this article to critically review all of the studies examining prophylaxis and preventative strategies for IC in the ICU, there are many studies and reviews on this topic.\textsuperscript{185–191} Identification of a sufficiently high-risk group or incidence has been an issue for most studies. A few meta-analyses have suggested potential mortality benefits with fluconazole prophylaxis; however, with an incidence of 1% to 2% in most ICU populations, more than 200 patients would need to undergo prophylaxis to prevent 1 infection. Therefore, it is necessary to consider prophylaxis strategies in high-risk individuals, pointing to the need for better risk stratification schemes in the ICU. If an at-risk group with an infection rate of at least 10% could be reliably identified, the number needed to treat to prevent 1 infection would be less than 20, and certainly this can be considered a potentially useful strategy for that specific patient group. The value of preemptive therapy has been best documented in the persistently neutropenic patient, and current guidelines suggest adding a broad spectrum antifungal agent in a neutropenic patient with persistent fever for 5 days despite broad spectrum antibiotics.\textsuperscript{192} A recent study examining non-neutropenic
patients did not find a benefit for the preemptive addition of fluconazole to persistently febrile patients in the ICU. Improved risk stratification schemes should allow for more directed preemptive therapy in high-risk groups. In addition, there is interest in monitoring nonculture-based diagnostic tests in critically ill patients (such as β-glucan) to identify patients on the threshold of sepsis. It is hoped that ongoing studies will help to answer these questions.

**SUMMARY**

Critical components in the management of antifungal sepsis that are clinician mitigated include (1) prompt antifungal therapy, (2) risk factor analysis to identify patients at higher risk than the general ICU population for IC and therefore in need of prophylactic or preemptive therapy given the current lack of prompt accurate diagnostics, (3) choice of the appropriate antifungal agent and dosing regimen, and (4) source control. Currently, until a species diagnosis or susceptibility is known, an echinocandin is recommended as first-line therapy for most patients with IC. PD studies suggest the currently recommended regimens would be useful for most infections. Once the species is identified, for *C. albicans*, *C. parapsilosis*, or *C. tropicalis* and the patient is responding to initial therapy, the appropriate therapy would include step down to fluconazole. For other species, the therapy should be directed based on susceptibility data. Source control, including line removal and evaluation for endophthalmitis is recommended for all patients with IC.

**REFERENCES**


