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Antifungal Dosing in Critically Ill Patients

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Abstract This article reviews appropriate dosing for antifungals and emphasizes factors specific to the critically ill patient, along with drug pharmacokinetics and pharmacodynamics. The rationale for doses of the echinocandins (caspofungin, micafungin, anidulafungin), triazoles (fluconazole, voriconazole, itraconazole, posaconazole), amphotericin B (including lipid formulations), and flucytosine are discussed.

Keywords Antifungals · Echinocandin · Caspofungin · Micafungin · Anidulafungin · Triazole · Fluconazole · Voriconazole · Itraconazole · Posaconazole · Amphotericin B · Lipid formulations · Flucytosine · Combinations · ICU · Critical care · Pharmacokinetics · Pharmacodynamics · Dose

Introduction

Fungal infections are on the rise in intensive care units (ICUs) because of invasive medical devices and resistance to standard therapies, causing the selection of pathogens. It is now well known that the time to effective treatment is important in determining outcomes of infected critically ill patients, and antifungal therapy is not an exception [1, 2]. If treatment is started at an inappropriate dose, however, the result may be diminished efficacy, increased frequency of resistance, or drug toxicity, all of which are avoidable poor outcomes. Patients in the ICU commonly have limited gastrointestinal absorption of oral medications, larger volumes of distribution because of fluid overload, decreased plasma protein levels due to critical illness, and diminished or fluctuating renal function [3]. Few studies address whether standard dosing regimens of antifungal agents need to be changed for critically ill patients. To optimize antifungal dosing for invasive fungal infections in these patients, health care providers must combine the available literature regarding general pharmacokinetic changes in critically ill patients and available pharmacodynamic data for different antifungal agents, as well as specific patient factors.

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Echinocandins

Echinocandins (caspofungin, micafungin, and anidulafungin) are available only as intravenous (IV) formulations because of their large molecular size. They inhibit the synthesis of 1,3 beta-glucan, a polysaccharide that is an important part of the fungal cell wall. Because of this distinct mechanism of action, they are less toxic to the human cell, as they lack this target [4••]. Echinocandins exhibit concentration-dependent fungicidal activity for all *Candida* species, but are fungistatic against *Aspergillus* species [5]. From a pharmacodynamic standpoint, the ideal maximum concentration is 10 times the minimum effective concentration [6]. Echinocandins can be dosed once daily because they have a long half-life of 10–40 h and exhibit dose-proportional plasma pharmacokinetics. Caspofungin and micafungin are more than 95% protein bound, whereas anidulafungin experiences 80% binding [7]. They all distribute well into major organ sites, including the brain. Concentrations in the cerebrospinal fluid are low, however, and lack of activity against *Cryptococcus neoformans* makes echinocandins a poor choice for fungal meningitis. Caspofungin and micafungin are metabolized in

the liver and then excreted in the feces (and a small amount in the urine); anidulafungin is degraded nonenzymatically in the plasma and then cleared by the liver, with less than 1% excreted unchanged in the urine [8].

Doses for the three commercially available echinocandins differ. The most commonly used echinocandin doses in critically ill patients when fungal infections are suspected include one 70-mg dose of caspofungin followed by 50 mg daily; 100 mg per day of micafungin; or a single dose of 200 mg of anidulafungin followed by 100 mg daily (Table 1). Loading doses of caspofungin and anidulafungin are used to reach steady state concentrations on the first day of treatment [7]. One might think that it would be necessary to decrease the dose of echinocandins frequently, as with other antifungals used in critically ill patients who have a high likelihood of end-organ damage, but a recent prospective study has proven otherwise [9]. When caspofungin was used clinically for either invasive candidiasis or aspergillosis, none of the patients suffered from worsening liver dysfunction or acute renal failure, regardless of their baseline hepatic or renal function. The use of this antifungal class is appealing in critically ill patients because none of the echinocandins need a dosage adjustment for renal insufficiency. Also, because the echinocandins are not dialyzable, no adjustment is needed for critically ill patients who are on dialysis. Caspofungin is the only echinocandin for which dosage adjustment is recommended when treating patients with hepatic dysfunction. In moderate liver failure (Child-Pugh scores 7–9), 35 mg daily should be used after the usual loading dose. Insufficient data exist to recommend dosing of caspofungin or micafungin in patients with more severe hepatic disease, but anidulafungin can be used at the normal dose in patients with Child-Pugh scores greater than 9 because little difference exists in plasma concentrations between these patients and patients with normal liver function [10]. High body weights and low serum albumin levels have affected echinocandin serum concentrations in some studies, but the clinical significance of these factors is not known because effective concentrations can persist for 96 h after one dose [11].

A recent multicenter, double-blind trial of high-dose caspofungin (150 mg/d) versus standard caspofungin treatment for adult patients with invasive candidiasis revealed that both regimens were effective and well tolerated [12•]. This was an important clinical finding because a paradoxic decrease in activity had been noted previously with higher doses in vitro [6]. The high-dose regimen had no better clinical outcomes and slightly more adverse events, however, so the utility of increasing echinocandin doses in the ICU remains to be seen. This type of study was possible because echinocandins as a class are known to be quite safe, causing only mild elevations in liver enzymes and bilirubin, along with occasional headaches, nausea, and vomiting. Rarely, they can cause a rash or anaphylactic reaction, but this effect is minimized by infusing each over at least an hour. In a meta-analysis comparing antifungal agents for invasive candidiasis, no significant differences in efficacy or adverse events were observed among the echinocandins [13]. Overall they have few drug interactions, as they are not significant substrates, inhibitors, or inducers of P-glycoprotein or the cytochrome P450 (CYP) enzyme system. This makes them attractive for use in critically ill patients that are receiving a number of other medications.

Over the past decade, echinocandins have emerged as an effective class of antifungals for treatment of ICU patients. Multiple studies have documented their clinical noninferiority to fluconazole, amphotericin B, liposomal amphotericin B, and even one another for the treatment of invasive candidiasis [14–16, 17••, 18••]. Although each echinocandin has different indications approved by government regulatory agencies, most experts consider their efficacy similar for the treatment of candidemia, esophageal candidiasis, intra-abdominal abscesses, peritonitis, and pleural space infections, as well as for empiric treatment of presumed fungal infections in febrile neutropenic patients and invasive aspergillosis in patients who are refractory to or intolerant of other therapies at the doses listed in Table 1.

Echinocandins have excellent in vitro activities against *Candida* species, and dosing may not need to be elevated beyond current recommendations. During a 6-year global surveillance period, the activities of all three remained consistent over time and over a wide geographic area, with most species having an MIC90 less than 0.25 mcg/mL [19]. The minimum inhibitory concentration (MIC) for *Candida parapsilosis* may be elevated for all echinocandins, however, because of amino acid polymorphisms in the major subunit of the drug target, glucan synthetase [20]. Guidelines recently updated by the Infectious Diseases Society of America (IDSA) recommend an echinocandin for the initial treatment of critically ill patients with suspected invasive candidiasis because of their reliable activity and predictable safety [21••]. For infections due to *Candida glabrata*, the echinocandin should be continued, but for infections with *C. parapsilosis*, fluconazole or a lipid formulation of amphotericin B is preferred. De-escalating from an echinocandin to fluconazole is also recommended for patients who are clinically stable and found to have other isolates that are likely susceptible, such as *Candida albicans* or *Candida tropicalis.*

Triazoles

Triazoles disrupt the fungal cell membrane via inhibition of cytochrome P450-dependent 14-α-demethylase. Inhibition of this enzyme prevents the conversion of lanosterol to

Table 1 Dosing of antifungals for common indications in critically ill adults with normal renal and hepatic function

Drug and route of administration	Candidemia and other invasive candidiasis	Invasive aspergillosis	Esophageal and oropharyngeal candidiasis	Empiric treatment of febrile neutropenia	Prophylaxis of high-risk patients with immunosuppression	Endemic dimorphic fungi	Cryptococcal meningitis
Caspofungin IV	70 mg×1, then 50 mg daily	70 mg×1, then 50 mg daily	70 mg×1, then 50 mg daily	70 mg×1, then 50 mg daily	70 mg×1, then 50 mg daily	Not indicated	Not indicated
Micafungin IV	100 mg daily	150 mg daily	150 mg daily	150 mg daily	50 mg daily	Not indicated	Not indicated
Anidulafungin IV	200 mg×1, then 100 mg daily	200 mg×1, then 100 mg daily	100 mg×1, then 50 mg daily	200 mg×1, then 100 mg daily	Unknown	Not indicated	Not indicated
Fluconazole IV/PO	800 mg (12 mg/kg)×1, then 400 (6 mg/kg) daily	Not indicated	200–400 mg daily	Not indicated	400 mg daily	Coccidioidomycosis only: 400–800 mg daily	800 mg/d with AmB or 800–2000 mg with 5-FC and 400 mg/d step-down monotherapy
Voriconazole IV/PO	6 mg/kg q 12 h×2, then 3–4 mg/kg q 12 h	6 mg/kg q 12 h×2, then 4 mg/kg q 12 h	200 mg q 12 h	6 mg/kg q 12 h×2, then 3–4 mg/kg q 12 h	400 mg q 12 h×2, then 200 mg q 12 h	Not indicated	Not indicated
Itraconazole PO	Not recommended	200 mg q 8 h×3, then q 12–24 h	200 mg daily	Not recommended	200 mg q 12 h	200 mg q 8 h×3, then q 12–24 h	Not recommended
Posaconazole PO	Not recommended	200 mg q 6 h	400 mg q 12 h	Not recommended	200 mg q 8 h	200 mg q 6 h, then 400 mg q 12 h	Not indicated
Amphotericin B IV	0.5–1 mg/kg daily	1–1.5 mg/kg daily	0.3 mg/kg daily	0.7 mg/kg daily	0.1–0.5 mg/kg daily	0.5–1 mg/kg daily	0.7–1 mg/kg daily±5-FC
Lipid formulation amphotericin B IV	3–5 mg/kg daily	3–5 mg/kg daily	3–5 mg/kg daily	3–5 mg/kg daily	1–3 mg/kg daily	3–5 mg/kg daily	4–6 mg/kg daily±5-FC

AmB amphotericin B, *5-FC* flucytosine, *IV* intravenously, *PO* orally, *q* every

ergosterol, leading to the accumulation of methyl sterols and ultimately resulting in disruption of fungal cell growth and replication [8, 22, 23]. Each of the four triazole antifungals (fluconazole, voriconazole, itraconazole, and posaconazole) have differing affinities for the 14-α-demethylase enzyme, leading to differing potencies against *Candida species and differences in fungistatic and fungicidal activity against various mycoses [22].*

In *Candida* species, triazole antifungals most often exhibit fungistatic activity with efficacy correlating to an area under the curve (AUC)/MIC≥25 [8, 24]. With regards to filamentous fungi, most data surround voriconazole, itraconazole, and posaconazole in the treatment or prevention of *Aspergillus* infections. Minimum plasma concentrations (Cmin) correlate with efficacy against *Aspergillus* species, with a Cmin greater than 500 ng/mL required for voriconazole and itraconazole; posaconazole requires a Cmin ranging from 700 to 1,500 ng/mL [24]. Each triazole has varying pharmacokinetic features and varying fungal activity, leading to special dosing considerations for critically ill patients.

Fluconazole

Fluconazole has activity against most *Candida* species (except *Candida krusei*, owing to intrinsic resistance, and some strains of *C. glabrata*, owing to about 20% acquired resistance) [25, 26]. Fluconazole is recommended as a first-line treatment option for some nonneutropenic patients with suspected or proven candidemia, but usually not for those who are critically ill. It would be appropriate treatment for patients with mild-to-moderate illness and no previous exposure to azole antifungals or risk factors for *C. glabrata*. Fluconazole is most useful as step-down therapy from echinocandins or amphotericin B in patients with susceptible organisms [21••]. Fluconazole remains the systemic drug of choice for treatment of oral candidiasis (100–200 mg/d) or esophageal candidiasis (200–400 mg/d) [21••]. It is also used in treating coccidioidomycosis (400–800 mg/d) and *Cryptococcus neoformans* infections [27, 28•]. For critically ill patients with cryptococcal meningitis, fluconazole is most often used as step-down consolidation therapy (400 mg/d for 8–10 weeks) or suppressive maintenance (200 mg/d for 6–12 months), but it can be combined with amphotericin B, replacing flucytosine during induction therapy (Table 1) [29]. A 1200-mg daily dose has been shown to be as well tolerated as 800 mg for primary monotherapy if needed, and the safety of fluconazole is illustrated in the IDSA treatment guidelines for cryptococcal disease, in which doses up to 2,000 mg/d are recommended [28•, 30].

For critically ill patients with invasive candidiasis, a fluconazole loading dose of 800 mg or 12 mg/kg, followed by 400 mg or 6 mg/kg daily, is recommended [21••, 22]. The loading dose allows steady state concentrations to be reached by day 2 of therapy [31]. Dosing in obese patients should be based on actual body weight when possible [32]. Appropriate fluconazole dosing becomes an important factor for optimal activity against *Candida* species. A 24-hour AUC/MIC less than 25 led to treatment failure in less than 10% of patients, based on six fluconazole studies [24, 33••]. To attain this goal, doses of 6 mg/kg daily are needed for isolates with susceptible MICs no higher than 8 mcg/mL, whereas doses of 12 mg/kg daily are needed for isolates with MICs of 16–32 mcg/mL in the susceptible dose–dependent range [24]. With AUC/MIC attainment so dependent on appropriate fluconazole dosing, another study in patients with candidemia assessed fluconazole dosing based on IDSA guidelines. Suboptimal empiric therapy was defined as doses less than 6 mg/kg, as occurred in 55% of patients with documented candidemia. Factors such as increased weight and a creatinine clearance greater than 50 mL per minute were independent variables that increased the risk of inadequate therapy [34].

Many of fluconazole's pharmacokinetic factors need to be considered when deciding a dose for a critically ill patient. Most patients will be started on IV fluconazole initially because of decreased gastrointestinal motility, but the oral formulation has greater than 90% oral bioavailability, allowing for an easy transition from IV to oral therapy. Another advantage in critically ill patients is that oral absorption is unchanged in patients receiving proton pump inhibitors or H2 antagonists, as well as in patients receiving doses via a gastric tube [35]. Fluconazole has a lower volume of distribution and minimal protein binding when compared with other triazoles, but it still reaches therapeutic levels in the central nervous system (CNS) and other tissues [23, 35]. It is primarily excreted by the kidneys, making it the most useful antifungal for treatment of candiduria. If *C. glabrata* or pyelonephritis is suspected, then 400 mg daily should be considered; otherwise 200 mg is sufficient. With 60% to 70% of the drug excreted unchanged in the urine, a dose adjustment is needed for patients with renal dysfunction who are not on dialysis [23]. For patients with creatinine clearance less than 50 mL per minute, the daily dose should be reduced by 50% or the normal dose should be given every 48 h. Because of the low degree of protein binding, fluconazole is extensively removed by dialysis, with 25% to 40% of the dose removed in a 4-hour period [35]. For patients on intermittent hemodialysis, 100% of the dose should be given after each dialysis session [35]. The amount of fluconazole removed increases in continuous renal replacement therapy (CRRT). The recommended dose depends on the type of CRRT used. Continuous venovenous hemofiltration (CVVH) requires doses of 200 to 400 mg (3–6 mg/kg) every 24 h; continuous

venovenous hemodialysis (CVVHD) requires doses of 400 to 800 mg (6–12 mg/kg) every 24 h; and continuous venovenous hemodiafiltration (CVVHDF) requires 800 mg (12 mg/kg) every 24 h [36•]. Dosage adjustment for hepatic impairment is not necessary because of the high degree of renal clearance. Fluconazole is not metabolized via the CYP450 system but does have inhibitory activity on CYP-2C9 and CYP-3A4, leading to drug interactions, although fewer significant interactions occur than are seen with voriconazole and itraconazole [35, 37•, 38].

Voriconazole

All *Candida* species, including *C. krusei* and *C. glabrata*, have the potential to be susceptible to voriconazole, although some cross-resistance does exist with fluconazole. *Aspergillus* species and rare molds such *Scedosporium* and *Fusarium* species also can be treated with voriconazole. Voriconazole is a first-line drug of choice for invasive aspergillosis and is considered as an alternative or step-down therapy for *Candida* infections [4••, 21••]. These indications, as well as its broad spectrum of activity, make voriconazole a relatively common therapy in critically ill patients. It is available in both IV and oral forms and has high oral bioavailability (>90%), which allows for ease in conversion of therapy [35]. For critically ill patients with invasive fungal infections, two 6 mg/kg doses of IV voriconazole are given 12 h apart on day 1, followed by 4 mg/kg IV twice daily, which can then be changed to oral therapy once the patient is stabilized and improving. With the IV loading dose, steady state is reached within 24 h; without the loading dose, it would take 5 days to 6 days to reach steady state [23]. Although it is not affected by stomach acid, one limitation of the oral form is that the bioavailability can be decreased by high-fat foods. The oral tablet should therefore be given 1 h before meals or 3 h after meals to optimize absorption. Continuous enteral supplementation ideally should be temporarily interrupted to allow optimal absorption of voriconazole [23, 35].

Voriconazole has a large volume of distribution with high tissue penetration, including excellent lung, CNS, and vitreous concentrations [21••, 35]. It is moderately protein bound (58%) and is extensively metabolized in the liver, primarily via CYP-2C19 [23, 35]. As a result, voriconazole exerts potent inhibition of enzymes such as CYP-3A4 and CYP-2C9, leading to numerous interactions with other drugs. In patients with severe hepatic impairment, dosage adjustments are necessary: the standard loading dose is still given, but it is followed by maintenance doses of only 2 mg/kg twice daily. Excretion of inactive metabolites occurs via the kidneys, with smaller amounts eliminated via the feces [35]. In patients with renal dysfunction or intermittent or continuous hemodialysis, no dosage adjustment is necessary for the oral formulations, but the IV formulation is contraindicated for patients with creatinine clearance less than 50 mL/min because of concerns regarding accumulation of the cyclodextrin carrier vehicle used in the IV preparation, rather than proven toxicity of the active drug itself [23, 35].

As experience with voriconazole increases, interpatient and intrapatient variability in voriconazole levels has become an evident problem, increasing the need for therapeutic drug monitoring. The fluctuation in levels can be attributed to various factors, including variable patient pharmacokinetics due to critical illness, drug interactions, or unpredictable differences in CYP-2C19 activity due to genetic factors associated with polymorphisms in this enzyme. About 15% to 20% of the Asian population has decreased CYP-2C19 activity, compared with about 1% to 3% of Caucasians [23, 35, 39•]. Because these factors can make levels vary widely, therapeutic drug monitoring is recommended for patients at risk of adverse effects or not responding to voriconazole therapy. Trough concentrations drawn after 2 days to 3 days of therapy should be within the range of 2 mg/L to 6 mg/L [8].

Itraconazole

Itraconazole covers a wide range of invasive mycoses, including *Candida* species, *Aspergillus* species, and endemic fungi. Despite its large spectrum of activity, itraconazole's role in the most severe infections is limited and it should be used only as step-down, alternative, or salvage therapy because of its unpredictable and complex pharmacokinetic profile. It is now available only in oral formulations. Dosing recommendations for treating invasive infections include a loading dose of 200 mg three times a day for 3 days, followed by 200 mg once or twice daily. The loading dose reduces the time it takes to reach steady state, usually 7–14 days without use of the loading dose because of its long elimination half-life (24 h) [23]. Despite the loading dose, concerns remain regarding attainment of steady state owing to various complex pharmacokinetic factors.

The oral forms of itraconazole, both capsules and solution, are not readily absorbed, although the solution provides greater bioavailability than the capsules because its cyclodextrin carrier vehicle increases hydrophilicity. The capsule formulation is best absorbed in an acidic environment, so it is recommended to be taken with food or a cola beverage. Acid-suppressive medications (antacids, H2 antagonists, and proton pump inhibitors) significantly reduce absorption and can lead to subtherapeutic levels. In contrast, absorption of the oral solution is optimal in an empty stomach [23, 35]. In the ICU, patients are commonly

in need of stress ulcer prophylaxis and may be receiving continuous enteral nutritional supplementation via a gastric tube; both of these may compromise therapy by altering itraconazole levels.

Itraconazole is extensively metabolized in the liver via the cytochrome-mediated pathways (primarily CYP-3A4) to an active metabolite, hydroxyitraconazole, and exerts potent CYP450 inhibition leading to numerous drug interactions [8, 35]. It is excreted primarily through the feces, so dosage adjustment is not needed for renal impairment or hemodialysis. The increased elimination half-life in the setting of severe hepatic impairment warrants dosage adjustments.

Because of its complex pharmacokinetics and the wide interpatient and intrapatient variability in levels due to various factors, therapeutic drug monitoring for both efficacy and toxicity is recommended for itraconazole when it is used in critically ill patients. Trough levels drawn after 5–7 days of therapy should be greater than 1 mcg/mL for therapeutic doses and greater than 0.5 mcg/mL for prophylaxis, as measured by high-performance liquid chromatography [39•].

Posaconazole

Posaconazole was approved by the US Food and Drug Administration (FDA) in 2006 for prophylaxis of invasive candidiasis and aspergillosis in severely immunocompromised patients at high risk of developing these infections. Despite the limited approval, it has a spectrum of activity that includes many invasive fungal infections, including endemic dimorphic fungi, zygomycetes, and *Fusarium* species. For prophylaxis, a dose of 200 mg given three times a day is recommended, but for treating invasive fungal infections, 800 mg should divided two to four times a day. It is important to note that the daily dose cannot all be given at one time because of saturable absorption. Dosage adjustments for renal and hepatic impairment are unnecessary because posaconazole is excreted primarily as unchanged drug in the feces. It has a large volume of distribution with high tissue penetration into most tissues, except for the CNS, although it has been used successfully in patients with CNS fungal infections [35]. It is not metabolized through the CYP450 enzyme system, but it is a potent inhibitor of CYP-3A4, leading to numerous drug interactions.

Unfortunately, because of its pharmacokinetic properties, posaconazole has a limited role as empiric therapy in patients who are critically ill. The highly lipophilic structure limits the development of an IV formulation, leaving only an oral option at this time. This oral suspension must be administered with food or liquid nutrition to optimize absorption, and recent data provide evidence that H2 antagonists and proton pump inhibitors may decrease posaconazole levels [23, 35]. Both of these limitations are considerations and challenges in treating critically ill patients in the ICU. In addition to limited forms and bioavailability, the saturable gastrointestinal absorption prevents the use of a loading dose at the initiation of therapy. With an elimination half-life of about 24 h, steady state without a loading dose usually is not reached for 7–10 days [23]. This time lag limits the use of posaconazole as an empiric agent, but it can be an option for treating resistant fungi or as salvage therapy in critically ill patients who are intolerant of other antifungal agents.

Amphotericin B

Amphotericin B is a polyene antifungal that consistently exerts fungicidal activity by attaching to sterols in the cytoplasmic cell membrane, leading to increased permeability. The result is concentration-dependent pharmacodynamics with a long post-antifungal effect that allows for infrequent dosing [24]. The best activity occurs at 4 to 10 times the organism's MIC, but it may plateau with repeated exposure, and only a fraction of amphotericin B is microbiologically active in tissue, regardless of plasma concentrations [40, 41]. Little else is known about its pharmacokinetic properties, even though the conventional formulation known as amphotericin B deoxycholate (AmBd) has been used in the United States since 1957. The metabolism and route of elimination for amphotericin B are not well understood. Because it is not absorbed orally, it is administered intravenously or occasionally intrathecally.

Although a dosage range exists for conventional amphotericin B (0.25–1.5 mg/kg per day), the usual dose is 0.7 mg/kg IV daily unless otherwise noted. Historically, the cumulative dose was monitored for a goal of 1.5–2.5 g. It was originally thought that a dosage of 0.3 mg/kg per day would be effective for all fungal infections, but it is now understood that this dose is suited only for treatment of minor infections such as urinary or esophageal candidiasis or for prophylaxis in immunocompromised patients [42]. Because of the improved safety of newer agents such as azole and echinocandin antifungals, amphotericin B is rarely used for prophylaxis or treatment of *Candida* infections, although it is still an effective salvage regimen in critically ill patients [43]. The role of amphotericin B lies in its broad spectrum when fungal infection is suspected but a specific pathogen has not been identified, such as for empiric treatment of fever in a neutropenic host. Antifungal therapy should be initiated in these patients if no response is noted after use of broad spectrum antibiotics. Because of widespread prophylaxis with azole antifungals and the

possibility of molds unresponsive to echinocandins, amphotericin B is well suited for use in this situation.

Amphotericin B is the drug of choice for cryptococcal meningitis and it also should be considered as initial treatment for endemic mycoses in critically ill patients. Induction therapy with 0.7 mg/kg per day for 2 weeks is the standard treatment (with flucytosine for Cryptococcal meningitis if possible) when used for these infections, but 1 mg/kg per day eliminated *Cryptococcus neoformans* more rapidly in one study [44]. Intrathecal doses of amphotericin B ranging from 0.1–1.5 mg (typically 0.5 mg) can be given as well if the CNS is infected, but this is usually given only to the most severely ill patients with refractory infections. *Aspergillus* species and zygomycosis also respond to amphotericin B, but surgery and higher doses (1–1.5 mg/kg per day for several months) are often required to achieve full resolution [45•]. High doses and long durations of this drug are more likely to cause nephrotoxicity, however [46]. Amphotericin B has a greater affinity for fungal ergosterol than for mammalian cholesterol, but its toxicity is not entirely selective. In patients with diminished renal function, the indicated dose may be decreased 50% (or ideally given every other day) to prevent further nephrotoxicity. Amphotericin B is poorly dialyzed, so no dosage change is needed in patients receiving hemodialysis or CRRT. In all patients, the dose should be infused over 4–6 h to reduce acute toxicities such as fever, chills, rigors, and cardiac arrhythmias. There is no evidence that additional distribution takes place in adipose tissue in obese patients, so dosing based on an ideal body weight can be used [32].

There are three lipid formulations of amphotericin B designed to limit the toxicities associated with the conventional form. Released in the 1990s, amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex (ABLC), and liposomal amphotericin B (L-AmB) have all shown efficacy similar to AmBd. The usual doses—3–5 mg/kg given as a single daily IV infusion—differ from AmBd dosing. They can also be infused more rapidly than conventional amphotericin B. ABLC and L-AmB can be given over 2 h, but ABCD should be administered no faster than 1 mg/kg per hour initially because its rates of infusion-related reactions are higher than those for the other lipid forms. No empiric dosage adjustment is indicated based on age or renal impairment for lipid formulations of amphotericin B [47]. Higher doses of L-AmB have been used for cryptococcal meningitis (6 mg/kg per day) and zygomycosis (10–15 mg/kg per day), although these doses have not been validated [45•, 48]. The AmBiLoad trial is the only randomized study of high loading doses for liposomal amphotericin compared with a standard regimen [49••]. To treat invasive aspergillosis, patients in this study received either 3 mg/kg or 10 mg/kg per day for 2 weeks and then all were administered 3 mg/kg per day. There was no difference in efficacy between the two groups, but nephrotoxicity and hypokalemia were significantly more common with the higher-dose regimen.

Flucytosine

Flucytosine is a pyrimidine analogue that inhibits DNA synthesis after it is taken up into cells by an enzyme specific to fungus. It is used for the treatment of cryptococcal meningitis in combination with another agent (usually amphotericin B) because of the rapid development of resistance when flucytosine is used by itself. This combination of therapy is associated with faster rates of cerebrospinal fluid clearance than amphotericin B alone or with fluconazole [50]. Fluconazole in doses up to 2,000 mg daily has also been combined with flucytosine to create an entirely oral regimen [51]. Optimizing the dose of flucytosine is important because the chemotherapeutic effect of flucytosine may cause significant bone marrow suppression. Its time-dependent pharmacodynamic activity requires that it be divided into four equal doses throughout the day. The pharmacodynamic goal is to exceed the organism's MIC for 40% of the dosing interval [24]. Traditionally, 150 mg/kg per day had been used in patients with normal renal function, but this dosage led to toxic plasma concentrations greater than 100 mcg/mL [42]. Lower doses of 75–100 mg/kg per day are appropriate when used in conjunction with a second antifungal agent [28•].

Conclusions

Appropriate dosing of antifungals for critically ill patients should be based on pharmacokinetic, pharmacodynamic, and patient-specific factors. Appropriate dosing can be just as important to outcomes as starting effective therapy in a timely manner.

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- • Of importance
- •• Of major importance

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