

## Overview of antifungal dosing in invasive candidiasis

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In the past, most antifungal therapy dosing recommendations for invasive candidiasis followed a ‘one-size fits all’ approach with recommendations for lowering maintenance dosages for some antifungals in the setting of renal or hepatic impairment. A growing body of pharmacokinetic/pharmacodynamic research, however now points to a widespread ‘silent epidemic’ of antifungal underdosing for invasive candidiasis, especially among critically ill patients or special populations who have altered volume of distribution, protein binding and drug clearance. In this review, we explore how current adult dosing recommendations for antifungal therapy in invasive candidiasis have evolved, and special populations where new approaches to dose optimization or therapeutic drug monitoring may be needed, especially in light of increasing antifungal resistance among *Candida* spp.

### Introduction

A growing body of evidence suggests that antifungal therapy is frequently underdosed in treatment of invasive candidiasis, especially in critically ill patients.<sup>1</sup> In a pharmacokinetic point prevalence study from 68 European ICUs, Sinnollareddy *et al.*<sup>2</sup> found that one-third of fluconazole-treated patients failed to achieve minimum recommended pharmacokinetic/pharmacodynamic (PK/PD) target exposures, a factor previously identified in several retrospective studies as an independent risk factor for death.<sup>3–5</sup> Drug exposures of anidulafungin and caspofungin were also variable or lower, on average, compared with exposures previously reported for healthy subjects. Recently, Jullien *et al.* reported that drug exposures among patients enrolled in a placebo-controlled trial of micafungin empirical therapy for invasive candidiasis were 50% lower than the values reported for healthy subjects, and 25% lower compared with hospitalized non-ICU patients.<sup>6,7</sup>

A possible silent epidemic of antifungal underdosing in hospitals among patients with invasive candidiasis is troubling for several reasons. First, the most commonly used agents, echinocandins and fluconazole, are well tolerated by patients even at much higher doses. Therefore, the risks versus benefits of using higher doses clearly favour more aggressive dosing for invasive candidiasis, where crude mortality rates still approach 40% even with effective therapy.<sup>8</sup> Second, insufficient dosing of triazoles has been linked to the emergence of resistance,<sup>9</sup> and *Candida* isolates with acquired multidrug resistance to fluconazole and echinocandins are increasing in frequency, with reported rates as high as 25%–30% when isolates are tested from deep tissue sites or mucosa after azole or echinocandin treatment.<sup>8,10–12</sup> Finally, antifungal underdosing could theoretically favour the emergence and

spread of MDR *Candida glabrata* and *Candida auris* in the critically ill and severely immunocompromised populations.<sup>13,14</sup>

In this article, we will review our current scientific rationale of antifungal dosing for invasive candidiasis, and summarize recent data concerning subpopulations of adult patients at risk for invasive candidiasis where dosing must be altered. We will also summarize adult patient-specific considerations that must be addressed when individualizing therapy and antifungal dosing for invasive candidiasis.

### Pharmacodynamic basis for antifungal dosing

#### Triazoles

Fluconazole was developed during the 1980s and first approved for clinical use in 1990. The drug quickly became the preferred agent for preventing and treating oral oesophageal candidiasis in patients with AIDS at a time before the availability of HAART. Fluconazole was the only available antifungal with predictable oral absorption and limited adverse effects. Intravenous fluconazole was also proved to be as effective as and less toxic than amphotericin B deoxycholate for the treatment of invasive candidiasis.<sup>15</sup> However, long-term treatment with fluconazole, which was necessary in patients with advanced AIDS and persistently low CD4+ counts, inevitably led to relapsing oesophageal candidiasis that failed to respond to conventional fluconazole doses (100–400 mg/day).<sup>16</sup> In some cases, fluconazole failures were linked to breakthrough infection caused by isolates with elevated MICs. However, many patients with relapsed oropharyngeal candidiasis would often still respond to higher doses of fluconazole.<sup>17</sup>

**Table 1.** PK/PD properties of antifungal agents for invasive candidiasis

Antifungal	Activity against <i>Candida</i> spp.	PK/PD parameter associated with treatment efficacy	PK/PD references
Polyenes	fungicidal		
DAmB		$C_{max}/MIC >10$ $AUC/MIC >100$ (varies depending on tissue infection site)	Andes et al., 2001 <sup>57</sup> Andes et al., 2006 <sup>56</sup>
LAmB		$C_{max}/MIC >40$	Hong et al., 2006 <sup>60</sup>
Triazoles	fungistatic	$fAUC/MIC 25-100$	Andes and van Ogtrop, 1999 <sup>20</sup> Louie et al., 1998 <sup>21,122</sup>
fluconazole			Andes et al., 2004 <sup>24</sup>
itraconazole			Andes et al., 2003 <sup>23</sup>
voriconazole			Lepak et al., 2013 <sup>22</sup>
posaconazole			Lepak et al., 2015 <sup>51</sup>
isavuconazole			Andes et al., 2003 <sup>37</sup>
Echinocandins	fungicidal	$fAUC/MIC >20$ ( <i>C. albicans</i> )	Andes et al., 2008 <sup>40</sup> and 2011 <sup>48</sup> Andes et al., 2010 <sup>38</sup>
anidulafungin			
caspofungin			
micafungin		$fAUC/MIC >7$ ( <i>C. glabrata</i> , <i>C. parapsilosis</i> )	Gumbo et al., 2007 <sup>45</sup> Andes et al., 2008 <sup>39</sup> Hope et al., 2007 <sup>123</sup> Petraitiene et al., 2015 <sup>43</sup>
Pyrimidine analogues	fungistatic	$T_{>MIC} 40\%$	Andes and van Ogtrop, 2000 <sup>61</sup> Hope et al., 2007 <sup>62</sup>
flucytosine			

By 1997, the National Committee for Clinical Laboratory Standards (now Clinical Laboratory Standards Institute, CLSI) had developed susceptibility breakpoints for interpretation of fluconazole MICs performed using a proposed standardized broth microdilution method.<sup>18</sup> Breakpoints for fluconazole included a novel 'susceptible-dose dependent' (SDD) category based on the clinical experience described above, where higher doses of fluconazole (12 mg/kg or 800 mg per day) were recommended for isolates with MICs ranging from 8 to 32 mg/L.<sup>19</sup>

The concept of a 'pharmacodynamic' SDD breakpoint was later supported by studies in animal models of invasive candidiasis that explored how changes in the dosing interval affected fluconazole efficacy over a wide range of doses. Andes and van Ogtrop<sup>20</sup> and Louie et al.<sup>21</sup> independently demonstrated that a fluconazole free-drug 24 h AUC to MIC ratio ( $fAUC/MIC$ ) of 25–50 was associated with a 50% reduction in fungal tissue burden in neutropenic mice with disseminated candidiasis. This PK/PD target was roughly equivalent to maintaining fluconazole concentrations above the MIC throughout the entire dosing interval (i.e.  $1 \times MIC \times 24 \text{ h} = AUC/MIC 24$ ) (Table 1). Subsequent studies confirmed that an  $fAUC/MIC$  target of 25–50 was predictive of efficacy for other triazoles (voriconazole, posaconazole, isavuconazole) if free (non-protein-bound) concentrations were considered.<sup>22–24</sup> An  $fAUC/MIC$  target of 25–50 was also confirmed to produce 50% reduction in tissue fungal burden among other *Candida* species with different resistance profiles and/or resistance mechanisms.<sup>25</sup>

When the outcomes of oesophageal candidiasis treatment were analysed according to the MIC of the infecting isolate, fluconazole treatment was successful in 91%–100% of treated patients

when the estimated  $fAUC/MIC$  surpassed 25, but was only 27%–35% successful in patients with a  $fAUC/MIC <25$ .<sup>26</sup> Most patients with normal body habitus and renal function could achieve  $fAUC/MIC >25$  up to a fluconazole MIC of 8 mg/L, but doses of 12 mg/kg/day (800 mg) were confirmed to be important for achieving this PK/PD target for SDD isolates (MIC 8–32 mg/L).<sup>19</sup>

Multiple observational studies have since documented a link between fluconazole  $fAUC/MIC$  and the outcomes of invasive candidiasis.<sup>3,5,26–31</sup> Given the nearly 1:1 linear relationship between fluconazole dose and AUC,<sup>32</sup> investigators have also reported that fluconazole dose/MIC  $>100$  was an independent predictor of treatment success when MICs were determined using the EUCAST methodology.<sup>27,29,31</sup>

A fluconazole dose/MIC target of 100 was subsequently used as the basis for proposal of a EUCAST susceptibility breakpoint for fluconazole of  $\leq 2$  mg/L.<sup>33</sup> The CLSI later adopted this same MIC susceptibility cut-off when it was shown that the lower breakpoint had improved sensitivity for detecting *C. albicans* that harbour acquired resistance mechanisms.<sup>34</sup> Now, standard dosages of fluconazole (400 mg/day) are considered to have a higher probability of treatment failure when the 24 h fluconazole MIC is  $\geq 4$  mg/L.<sup>34</sup>

### Echinocandins

Caspofungin, the first echinocandin approved for clinical use, entered clinical trials in 1995 when there was still a dire need for new therapies active against fluconazole-resistant oral-oesophageal candidiasis.<sup>35</sup> Early pharmacokinetic studies suggested that a 70 mg loading dose of caspofungin followed by 50 mg daily would result in levels  $>1$  mg/L on the first day of

therapy, a target that exceeded the MIC of 90% of the most clinically relevant *Candida* species.<sup>35,36</sup>

Subsequent animal studies provided a clearer description of the PK/PD behaviour of echinocandins during the treatment of invasive candidiasis. Andes and colleagues examined the effects of altered dosing intervals and escalating doses for a novel glucan synthesis inhibitor, HMR 3270, in a neutropenic murine model of disseminated candidiasis.<sup>37</sup> The investigators found that treatment outcome was strongly correlated with drug dose and organism MIC, with a total drug  $C_{max}/MIC$  3.72 or  $AUC/MIC >300$  suppressing *Candida* growth in the model. Maximal fungicidal effects were observed as the  $C_{max}/MIC$  approached 10.

Subsequent studies with caspofungin, micafungin and anidulafungin confirmed that 5- to 8-fold less drug was required to achieve similar reductions in *Candida* tissue fungal burden if echinocandins were administered as single dose.<sup>38-45</sup> In a direct comparison of caspofungin, micafungin and anidulafungin against different *Candida* species, Andes *et al.*<sup>38</sup> later reported that  $fAUC/MIC$  was highly predictive of treatment response for all three echinocandins, but  $fAUCs$  were lower for *C. parapsilosis* (mean, 7) and *C. glabrata* (mean, 7) compared with *C. albicans* (mean, 20). These species-specific PD targets later served as the basis (along with population MIC data) for unique CLSI and EUCAST *Candida* species-specific susceptibility breakpoints for the echinocandins.<sup>46,47</sup>

The clinical validity of echinocandin PK/PD targets was subsequently analysed in 493 patients with invasive candidiasis who received micafungin as part of the Phase 3 clinical trial.<sup>48</sup> A population PK model was used to estimate micafungin exposures and was validated in a subset of patients with available PK data. The investigators identified the following independent risk factors affecting cure: severity of illness, a micafungin total  $AUC/MIC >3000$  for all *Candida* species, or a total drug  $AUC/MIC >5000$  for non-*C. parapsilosis* species, an MIC  $<0.5$  mg/L, and a history of steroid use (Table 1). Patients with a micafungin total drug  $AUC/MIC >3000$  achieved clinical and mycological cure rates of 98%. Considering protein binding in humans, an  $AUC/MIC$  target  $>3000$  translates to a free drug ratio of 7.5, whereas the  $AUC/MIC >5000$  translates to a free drug ratio of 12.5.<sup>49</sup> When corrected for protein binding, the micafungin  $AUC/MIC$  targets identified in the clinical trials (7.5 and 12.5, respectively) were almost identical to free-drug micafungin  $AUC/MIC$  targets previously identified in neutropenic mice.<sup>38,45,50</sup>

Collectively, these data suggested that higher intermittent dosing would optimize the PD of echinocandin therapy.<sup>51</sup> This concept was tested in a randomized study of micafungin for oral oesophageal candidiasis that compared micafungin administered 150 mg daily with 300 mg dosed every other day.<sup>52</sup> The mycological response rate at the end of therapy was higher in patients who received the higher-dose, intermittent micafungin regimen (85% versus 79%, respectively,  $P=0.056$ ) with significantly lower relapse rates (6% versus 12%, respectively,  $P=0.05$ ).

More recently, Gumbo<sup>50</sup> described a patient with underlying immunodeficiency of unclear aetiology and a history of recurrent oesophageal candidiasis who was initially treated with a standard micafungin dose of 100 mg daily for 2 weeks. The patient was subsequently administered a single 700 mg dose in the following week, followed by 1400 mg doses every other week with liver function test monitoring 3 days after each dose. The patient tolerated the regimen for 12 weeks until she developed evidence of liver

function test abnormalities that was later attributed to injection of illicit drugs with acetaminophen. She later resumed the 1400 mg dosing every 2 weeks without elevation of liver enzymes.

Several studies have explored the potential efficacy and safety of higher-dose daily echinocandin regimens. The largest of these studies was performed by Betts and colleagues,<sup>53</sup> who performed a double-blind randomized trial in 204 patients with invasive candidiasis, with 104 patients receiving a standard 70 mg loading dose of caspofungin followed by 50 mg daily and 95 patients receiving 150 mg daily. A non-significant trend towards improved clinical and microbiological response was observed in patients receiving the higher-dose regimen, with overall response at day 10 of therapy of 94.5% versus 84% in the high- versus low-dose groups, respectively ( $\Delta 10.5\%$ , 95% CI 0.7%–20.9%). Mortality was similar in both groups at 8 weeks and no safety concerns were found for caspofungin at a dose of 150 mg/day. Notably, most patients in the trials ( $>70\%$ ) had lower APACHE II scores and had uncomplicated candidaemia (84%). This study was also performed prior to wider dissemination of echinocandin-resistant *C. glabrata*; therefore it is possible that differences between the two dosing groups may have been greater in more critically ill patients with a higher prevalence of resistant organisms.

Additional evaluations of dosing for current and novel echinocandins in development [e.g. rezafungin (CD101)] have been completed recently and are reviewed separately.<sup>54</sup>

### Amphotericin B lipid formulations

Lipid formulations of amphotericin B are recommended over conventional amphotericin B-deoxycholate (DAmB) for the treatment of invasive candidiasis except in resource-limited areas.<sup>55</sup> Each of the three lipid formulations [amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD) and liposomal amphotericin B (LAmB)] is complexed to a different lipid carrier system, exhibits different PK properties, and is 5- to 7-fold less potent than DAmB on a mg/kg basis depending on the tissue site analysed.<sup>56</sup> Studies comparing escalating doses and altering treatment intervals in invasive candidiasis have found that the  $C_{max}/MIC$  is the PD parameter that best correlates with DAmB treatment outcome in experimental invasive candidiasis,<sup>57</sup> with the  $AUC/MIC$  ratio and time above MIC less predictive of fungicidal activity. In disseminated candidiasis models, differences in the rates of *Candida* liver, spleen and lung fungal burden mirrored differences in tissue kinetics of amphotericin B measured by bioassay for each of the lipid amphotericin B formulations.<sup>56</sup>

Limited clinical data are available linking amphotericin B PK/PD to clinical endpoints. Restricted dosing and the limited MIC range for amphotericin against *Candida* species are factors that complicate clinical PK/PD studies.<sup>58</sup> Toxicity of higher DAmB doses may also obscure the benefit of higher drug exposures.<sup>59</sup> One paediatric study reported that a  $C_{max}/MIC >40$  was associated with maximal response during liposomal amphotericin B treatment,<sup>60</sup> which, after correcting for potency differences, is similar to the DAmB  $C_{max}/MIC$  of 10 reported in preclinical models of disseminated candidaemia.<sup>59</sup>

### Flucytosine

Flucytosine is occasionally used in combination with amphotericin B-based regimens for the treatment of CNS candidiasis, native

valve endocarditis or fluconazole-resistant urinary candidiasis.<sup>55</sup> Studies examining flucytosine PD in animal models of invasive candidiasis and cryptococcosis have shown that the percentage of time flucytosine concentrations surpass the MIC best predicts antifungal efficacy, with a % $T_{>MIC}$  of at least 40 required for fungistatic effect.<sup>61,62</sup> Therefore, lower doses but more frequent administration of the drug (e.g. 25 mg/kg every 6 h) optimizes PK/PD target attainment and reduces the risk of bone marrow toxicity, which is linked to peak concentrations >100 mg/L.<sup>63</sup>

## Patient-level considerations for dosing

### Triazoles

Fluconazole is still considered the preferred triazole for the step-down treatment of candidaemia in non-neutropenic critically ill patients by several guidelines, with voriconazole being a valuable alternative.<sup>64</sup>

Although moderately lipophilic in nature, fluconazole is the only triazole significantly eliminated by the renal route. Considerable interindividual PK variability of fluconazole was documented in a small cohort of critically ill patients ( $n = 21$ ) who were treated with a median dose of 400 mg/day. In 33% of these, drug exposure was insufficient to attain the PK/PD target of  $AUC/MIC > 100$ , in spite of a relatively low median creatinine clearance ( $CL_{CR}$ ) (45 mL/min).<sup>2</sup> Accordingly, it may be hypothesized that the risk of fluconazole underexposure with the fixed 400 mg/day dose may be even higher among patients with augmented renal clearance ( $CL_{CR} > 130$  mL/min).<sup>65</sup>

The PK of voriconazole was also assessed in critically ill patients after standard intravenous (iv) dosing (6 mg/kg loading dose and 3–4 mg/kg twice daily thereafter) in a prospective observational study involving 18 patients with different degrees of renal function (12 with normal renal function,  $CL_{CR} \geq 60$  mL/min, and 6 with moderate renal impairment,  $CL_{CR}$  40–55 mL/min).<sup>66</sup> Large interindividual variability in  $C_{min}$  was observed.  $C_{min}$  was outside the desired therapeutic range (1–5.5 mg/L)<sup>67</sup> in more than half of cases (56%), with 37% of patients having suboptimal exposure ( $\leq 1$  mg/L) and 19% having potentially toxic levels ( $> 5.5$  mg/L). The wide interindividual variability was unrelated to differences in renal function, in agreement with the fact that voriconazole is a non-renally cleared drug.

Voriconazole is a highly lipophilic drug that is almost completely metabolized by three CYP450 isoenzymes, namely CYP3A4, CYP2C9 and CYP2C19.<sup>68</sup> Voriconazole shows wide interindividual PK variability among several different types of patient populations. This is mainly due to the genetic polymorphism of CYP2C19, the primary enzyme involved in the elimination pathway of voriconazole. Importantly, the distribution of the genetic polymorphisms of CYP2C19 may vary greatly among the various racial/ethnic groups. It has been shown that up to one-third of Caucasians may be ultra-rapid metabolizers of CYP2C19, and may experience drug underexposure with therapeutic failure; conversely, up to 20% of Asians may be poor metabolizers and may experience drug overexposure with toxicity.<sup>68</sup>

The wide interindividual variability of voriconazole was confirmed in a very large study of real-life therapeutic drug monitoring (TDM). Among 14923 voriconazole  $C_{min}$  values, almost half were outside the desired range (39.2%  $< 1$  mg/L and 10.4%

$> 5.5$  mg/L).<sup>69</sup> The interindividual PK variability of voriconazole may become even wider during polytherapy owing to drug–drug interactions. It has been shown that co-medication with CYP450 inhibitors (i.e. proton pump inhibitors) and/or with CYP450 inducers (i.e. corticosteroids, phenobarbital, carbamazepine and rifampicin) may significantly influence voriconazole clearance.<sup>70,71</sup> TDM of voriconazole is recommended by several guidelines.<sup>67,72</sup> Therapeutic recommendations for the use of voriconazole for treatment based on CYP2C19 genotype have also been developed.<sup>73</sup>

Both fluconazole (at doses  $> 200$  mg/day) and voriconazole are potent inhibitors of CYP2C9, CYP2C19 and CYP3A4. This may cause overexposure during co-administration with drugs that are substrates of these CYP450 isoenzymes.<sup>74</sup> A recent study aimed at evaluating the prevalence of triazole drug–drug interactions among hospitalized adults who were identified within a database containing data from over 150 hospitals.<sup>75</sup> The study showed that 82% of hospitalizations with voriconazole use included the use of at least one drug that resulted in a severe drug–drug interaction. Management of these interactions should involve appropriate dosage adjustments when necessary, and TDM when available (e.g. immunosuppressive drugs).

The relatively high lipophilicity of the triazoles may ensure high penetration rates of these antifungals into deep tissues with a valid diffusion even through the anatomical barriers. These properties are clinically relevant in deep-seated *Candida* infections. Triazoles may achieve therapeutically relevant concentrations in several tissues, with tissue-to-plasma ratios of  $\geq 0.7$  in most cases, even in CSF and/or in cerebrum.<sup>76</sup> Both fluconazole and voriconazole were shown to concentrate in the aqueous humour,<sup>77,78</sup> and are therefore considered valuable agents in the treatment of *Candida* endophthalmitis. Likewise, it was recently shown the valuable intra-abdominal penetration of fluconazole into the bile and the ascites of three liver transplant patients ensured optimal PD exposure with successful clinical treatment of deep-seated candidiasis.<sup>79</sup>

### Echinocandins

The echinocandins are considered the first-line choice of treatment for candidaemia in non-neutropenic critically patients by several guidelines.<sup>64</sup> Anidulafungin, caspofungin and micafungin are highly protein-bound hydrophilic compounds, which are ultimately eliminated mainly through ubiquitous spontaneous degradation. The echinocandins are administered at fixed dosages (anidulafungin, 200 mg loading dose followed by 100 mg/day; caspofungin, 70 mg loading dose followed by 50 mg/day; micafungin, 100 mg/day) and are traditionally considered as drugs that are easy to manage in critically ill patients, thanks to the low potential for drug–drug interaction and to the non-renal and less extensive hepatic clearance.<sup>80</sup>

However, recent studies have raised questions concerning the appropriateness of fixed standard dosages of these antifungal agents in attaining optimal PK/PD targets against *Candida* infections in the critically ill patients. Caspofungin PK was assessed in 21 critically ill patients. All of the patients had moderate hepatic dysfunction (Child–Pugh class B) and most were severely hypoalbuminaemic ( $< 25$  g/L in 81% of cases). Caspofungin showed limited intra-individual and moderate inter-individual PK variability, with drug exposures comparable to those observed in other non-critically

ill patients. Although the authors concluded that ICU patients do not need higher dosages compared with other reference groups, it should not be overlooked that all of the study patients were affected by moderate hepatic dysfunction, namely a pathophysiological condition that was shown to increase caspofungin exposure. However, in critically ill patients with low albumin, the volume of distribution and clearance of echinocandins is likely increased.

The PK of anidulafungin in critically ill patients was assessed in 20 subjects, most of whom were elderly, underwent abdominal surgery and had *Candida* peritonitis.<sup>81</sup> No relationship between anidulafungin exposure, in terms of AUC, and disease severity scores [e.g. APACHE 2, simplified acute physiology score (SAPS), SOFA 2] or albuminaemia levels was found. However, anidulafungin exposure in this patient population was lower than that observed in the general patient population. This led the authors to conclude that, although no problem would be expected in the treatment of infections due to very susceptible strains of *C. albicans* or *C. glabrata*, conversely dosage adjustment based on TDM could be needed when dealing with *Candida* strains having higher MICs near to the clinical breakpoint. The presence of lower anidulafungin exposure compared with that in healthy volunteers or other patient populations was subsequently confirmed in another cohort of critically ill patients.<sup>82</sup>

The PK of micafungin was also found to be altered among 20 critically ill patients, most of whom were elderly and had moderate (Child–Pugh class B) or severe (Child–Pugh class C) hepatic dysfunction.<sup>83</sup> Micafungin PK was assessed twice, on day 3 ( $n = 20$ ) and on day 7 ( $n = 12$ ). The PK behaviour was similar on the two assessment days and overall micafungin exposure in these critically ill patients was lower than that in healthy volunteers, even if not significantly different from that of other reference populations. The authors suggested that higher than standard dosages could be considered in this setting, and that TDM might represent a helpful tool for optimizing patient care.

Their hydrophilic nature coupled with their high molecular weight prevent the echinocandins from achieving therapeutically effective concentrations in infection sites protected by anatomical barriers. Therefore, when dealing with *Candida* endophthalmitis or with CNS infections, echinocandin monotherapy should be avoided.<sup>84,85</sup>

### Amphotericin B lipid formulations

The PK of amphotericin B lipid formulations has never been investigated in critically ill patients with candidaemia and/or invasive candidiasis. However, according to the peculiar characteristics of these moieties, which are cleared from the bloodstream mainly by the reticulo-endothelial system, it is unlikely that the PK behaviour of these formulations would be affected by critical illness. Standard dosages up to 5 mg/kg/day should be appropriate even in this setting. When in presence of deep-seated complications, such as *Candida* endophthalmitis and/or of CNS infections, liposomal amphotericin B should be the preferred formulation. This is based on clinical experience and on evidence from preclinical animal models showing that the liposomal formulation achieved the highest concentrations in the aqueous humour, CSF and brain parenchymal tissue.<sup>86,87</sup>

### Flucytosine

Flucytosine PK have not been investigated in critically ill patients.<sup>88</sup> This antifungal agent has limited protein binding and is eliminated by glomerular filtration. Accordingly, it would be expected that dose intensification could be a valuable approach for avoiding sub-inhibitory concentrations in critically ill patients with augmented renal clearance. Flucytosine may achieve therapeutically relevant concentrations in the vitreous humour and in the CSF, and may therefore represent an option in combination therapy for the treatment of fungal infections located in the eye or in the CSF.<sup>88,89</sup>

## Special populations

### Renal impairment

Renal impairment may represent an important concern for adjusting maintenance dosages for those antifungals that normally are eliminated by the renal route.

Fluconazole is the only triazole that needs adjustments of the maintenance dose in relation to renal impairment. Since fluconazole undergoes glomerular filtration with partial tubular reabsorption, it has been recently documented that estimation of the glomerular filtration rate might not accurately predict fluconazole clearance, and this may interfere with correct dosage adjustments.<sup>90</sup> TDM was suggested as a helpful tool for optimizing fluconazole exposure in the setting of critically ill patients, especially when renal replacement therapies (RRTs) are applied.<sup>67</sup> An early study assessed the PK of fluconazole among 16 critically ill patients who underwent continuous veno-venous haemofiltration (CVVH).<sup>91</sup> The ultrafiltration flow rate was of 1000–2000 mL/h in predilution mode. The authors showed that fluconazole is very efficiently eliminated during CVVH and that a dosage of 800 mg/day would be needed to ensure appropriate drug exposure in this setting. The PK behaviour of fluconazole was recently assessed also in critically ill patients receiving prolonged intermittent RRT.<sup>92</sup> Monte Carlo simulations were performed in order to estimate the PTA of achieving an AUC/MIC ratio of 100 during the initial 48 h of antifungal therapy. It was shown that a fluconazole dosing regimen of 800 mg loading dose plus 400 mg twice daily (every 12 h or pre- and post-prolonged intermittent RRT) would be appropriate. Likewise, fluconazole PK was assessed during sustained low-efficiency dialysis (SLED-f), which is a technique increasingly being utilized in critically ill patients because of its practical advantages over continuous RRT.<sup>93,94</sup> It was shown that during a single SLED-f session of 6 h, 72% of fluconazole was cleared compared with the much lower clearance (33%–38%) reported during a 4 h intermittent haemodialysis session. The authors concluded that doses >200 mg/day should be required for attaining optimal PK/PD in patients undergoing SLED-f.

Voriconazole is a non-renally cleared triazole whose iv use is contraindicated in critically ill patients with  $CL_{CR} < 50$  mL/min. This recommendation is provided to prevent the accumulation of the sulphobutylether- $\beta$ -cyclodextrin (SBECD) vehicle, which is present in the iv formulation and which is predominately excreted by glomerular filtration. A prospective, open-label PK study was carried out among 10 critically ill patients receiving iv voriconazole while undergoing continuous RRT (CRRT). The aim was to verify whether CVVH (median total ultrafiltration rate of 38 mL/kg/h) may sufficiently remove SBECD to allow for the use of iv voriconazole

without significant risk of SBECD accumulation.<sup>95</sup> Voriconazole clearance was only minimal during CVVH, which conversely removed SBECD efficiently at a rate similar to the ultrafiltration rate. The findings allowed the authors to conclude that standard dosages of iv voriconazole can be utilized in patients undergoing CVVH without significant risk of SBECD accumulation.

The echinocandins are non-renal cleared drugs, and do not require dosage adjustments in the presence of renal impairment.<sup>96</sup> Recent studies assessed the PK behaviour of anidulafungin and of caspofungin in critically ill patients undergoing CRRT and confirmed that no dosage adjustment for these echinocandins is needed under these circumstances.<sup>97–99</sup>

Amphotericin B lipid formulations are not renally cleared and do not need any dosage adjustments, either in the presence of renal impairment or in the presence of CRRT.<sup>100</sup>

Flucytosine is eliminated by glomerular filtration, and proportional dosage adjustments are required in patients with renal impairment.<sup>88</sup> A recent case report provided evidence that dosing may be an issue for flucytosine in patients undergoing CRRT.<sup>101</sup>

### Hepatic impairment

Liver disease encompasses a wide range of both acute and chronic pathological changes that can alter the PK and tissue penetration of antifungal agents. Chronic cirrhosis is associated with changes in protein binding, altered volume of distribution, metabolism and altered renal clearance of many antibiotics and antifungals.<sup>102</sup>

Recommendations for antifungal dosing adjustment in patients with hepatic dysfunction, however, are not straightforward. Reduction of antifungal doses by one-third to one-half is recommended in the summary of manufacturers' product characteristics (SmPC) in patients with moderate to severe hepatic insufficiency (i.e. Child–Pugh class B or greater) receiving treatment with itraconazole, voriconazole, caspofungin and possibly posaconazole.<sup>103</sup> No dose adjustment is recommended for micafungin in patients with mild or moderate hepatic impairment.<sup>103</sup> No dose adjustment is needed for Child–Pugh scores of 7–9. For severe hepatic dysfunction (Child–Pugh scores of 10–12), increased micafungin clearance results in 7%–39% lower serum concentrations, but the clinical significance of this finding is unknown. Fluconazole is cleared primarily through glomerular filtration and does not require adjustment for liver dysfunction. Similarly, anidulafungin is degraded through a non-hepatic enzymatic process and does not have a dosage adjustment recommendation in patients with severe hepatic dysfunction. No specific recommendations are available for amphotericin B products, but given their limited metabolism, dosage adjustment in hepatic dysfunction is unlikely to be necessary.

A problem with these recommendations is that the Child–Pugh classification system was not developed to predict drug elimination capacity. The classification system is based on the two clinical features (encephalopathy and ascites) and three laboratory-based parameters (albumin, bilirubin and prothrombin time). Hepatic dysfunction is categorized into groups called A, B and C or 'mild', 'moderate' and 'severe', corresponding to 5–6, 7–9 and 10–15 scores, respectively. As a result, even subjects with a normal hepatic function are given a total score of 5 points (since each variable gives a score of 1 point even within the normal range) and would consequently be classified as having mild hepatic impairment.<sup>104</sup> Moreover, laboratory-based parameters used in

calculation of the Child–Pugh classification lack specificity for liver disease. For example, albumin levels may be influenced by inflammation and nutritional status and are often low in critically ill patients with sepsis. Bilirubin may be increased due to cholestasis, hepatocellular failure or haemolysis.<sup>104</sup> Hence, PK data used to define the dosing recommendation in patients with Child–Pugh B or C chronic alcoholic or viral liver cirrhosis may not be applicable to critically ill patients with organ dysfunction.

Several recent studies have suggested that hypoalbuminaemia, which could lead to a classification of 'moderately severe' Child–Pugh B, may be a risk factor for inadequate echinocandin exposure.<sup>6,105,106</sup> Caspofungin labelling includes a recommendation for reduction of maintenance doses from 50 mg daily to 35 mg daily in patients with Child–Pugh class B or greater liver dysfunction. However, Martial and colleagues<sup>106</sup> reported that dosage reduction following these guidelines in non-cirrhotic ICU patients resulted in inadequate caspofungin exposures, especially for isolates near the current susceptibility breakpoints (MIC 0.125 mg/L). The authors recommended that a higher maintenance dose of caspofungin, 70 mg/day, should be administered in ICU patients with Child–Pugh B liver dysfunction if the classification is driven primarily by hypoalbuminaemia.

### Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is a type of cardiopulmonary bypass, which is used to sustain temporarily cardiac and/or respiratory function in critically ill patients. It was shown that ECMO may significantly affect the PK behaviour of drugs by various mechanisms (sequestration in the circuit, increased volume of distribution and decreased drug elimination), even if a lack of predictability is of concern.<sup>107</sup> Voriconazole, being highly lipophilic, was shown to be significantly sequestered in the circuit,<sup>108,109</sup> so that TDM is recommended for optimal antifungal treatment under these circumstances.<sup>109</sup> Fluconazole, which is hydrophilic and renally cleared, may be significantly affected by haemodilution. Higher volume of distribution but similar clearance were observed in infants and children during ECMO when compared with historical controls not on ECMO.<sup>110,111</sup> Caspofungin was found to be affected by ECMO to a lesser extent.<sup>109</sup>

### Obesity

Specific dosing guidance for antifungals in obese patients remains limited. A general dosing recommendation for all triazole antifungals is not possible given the marked physicochemical and PK differences between agents in the same class. Population PK models devised in patient populations with BMI classifications of obese (30–40 kg/m<sup>2</sup>) and morbidly obese (>40 kg/m<sup>2</sup>) suggest that fluconazole should be dosed based on total body weight (12 mg/kg loading dose, followed by 6 mg/kg/day maintenance) adjusted for renal function,<sup>112</sup> whereas voriconazole should be dosed based on adjusted body weight.<sup>113,114</sup> Although fewer data are available for itraconazole, posaconazole and isavuconazole, their greater physicochemical similarity to voriconazole suggests that they should be similarly dosed based on lean body weight.<sup>115</sup>

Liposomal amphotericin B has limited distribution into adipose tissue and, given potential toxicity concerns with doses based on

**Table 2.** Overview of antifungal dosing in invasive candidiasis

Drug	Standard dose	Hepatic impairment	Renal impairment	CRRT	Obesity
Fluconazole	LD 800 mg 12 mg/kg day 1 → MD 400 mg (6 mg/kg/day) q24h. <sup>124</sup>	Limited data, no specific recommendations. <sup>103</sup>	100–200 mg q24h if $Cl_{Cr}$ < 50 mL/min; supplemental dose of 50–100 mg after IHD.	300–400 mg q12h. <sup>92</sup>	No dosage adjustment; dose on total body weight. <sup>118</sup>
Voriconazole	LD 6 mg/kg q12h day 1 → MD 4 mg/kg 12 h. <sup>124</sup>	Mild to moderate hepatic insufficiency (Child–Pugh Class A and B): 6 mg/kg q12h × 2 doses (load), then 2 mg/kg iv q12h. Monitor serum concentrations. <sup>103</sup>	No dosage adjustment.	No dosage adjustment. <sup>95</sup>	Dose based on adjusted body weight. <sup>116</sup>
Anidulafungin	LD 200 mg day 1 → 100 mg q24h. <sup>124</sup>	For Child–Pugh class A, B, or C: usual dose. <sup>103</sup>	No dosage adjustment.	No dosage adjustment. <sup>97</sup>	Increase the daily echinocandin dose by at least 25%–50% of the usual dose in patients weighing > 75 kg. <sup>118</sup>
Caspofungin	LD 70 mg day 1 → 50 mg q24h. <sup>124</sup>	For Child–Pugh score of 7–9, after initial 70 mg load on day 1, decrease daily dose to 35 mg q24h. <sup>103</sup> Recent studies have suggested dosages should not be reduced in ICU patients if Child–Pugh score driven by hypoalbuminaemia. <sup>106</sup>	No dosage adjustment.	No dosage adjustment. <sup>98</sup>	Increase the daily echinocandin dose by at least 25% to 50% of the usual dose in patients weighing > 75 kg. <sup>118</sup>
Micafungin	100 mg q24h. <sup>124</sup>	No dose adjustment needed For Child–Pugh score of 7–9. For severe hepatic dysfunction (Child–Pugh score of 10–12): increased micafungin clearance resulting in 7%–39% lower serum concentrations, but the clinical significance is unknown. <sup>103</sup>	No dosage adjustment.	No data. Usual dose likely.	Increase the daily echinocandin dose by least 25%–50% of the usual dose in patients weighing > 75 kg. <sup>118–120</sup> Alternative dosing formula proposed for patients up to 200 kg. Dose (mg) = patient weight + 42. <sup>119</sup>
Lipid formulation of amphotericin B	3–5 mg/kg q24h. <sup>124</sup>	No data. Usual dose likely. <sup>103</sup>	No dosage adjustment.	No dosage adjustment.	Dose based on lean body weight. <sup>118</sup>
Flucytosine	25 mg/kg q6h. <sup>124</sup>	No data. Usual dose likely. <sup>103</sup>	25 mg/kg q 24–48 h; supplementary dose of 20–50 mg/kg after IHD.	NA	Dose based on ideal body weight. <sup>118</sup>

LD, loading dose; MD, maintenance dose; IHD, intermittent haemodialysis; NA, not available.

total body weight in obese patients, doses should be calculated based on a patient's lean body weight.<sup>116</sup>

Body weight is an important variable influencing the volume of distribution and clearance of all three echinocandins.<sup>115</sup> Higher total body clearance of caspofungin has been reported among surgical ICU patients with a total body weight >75 kg.<sup>117</sup> An increase in the daily caspofungin maintenance dose of 25%–50% has been proposed for patients weighing >75 kg with severe infection.<sup>118</sup> In a PK study in patients with BMI <25, 25–40 and >40 kg/m<sup>2</sup>, micafungin clearance increased in proportion to weight in subjects weighing between 65 and 150 kg.<sup>119</sup> The investigators proposed a bedside formula for individualized micafungin dosing in obese patients up to 200 kg: dose (mg) = patient weight (kg) + 42.<sup>120</sup> Anidulafungin PK are also affected by weight. Lempers and colleagues reported that anidulafungin exposure was on average 32.5% lower in obese patients (BMI >40 kg/m<sup>2</sup>) compared with the general patient population.<sup>121</sup> Although more data are needed, these studies collectively suggest that daily echinocandin doses should be increased by 25%–50% in patients weighing >75 kg, especially in critically ill patients with invasive candidiasis.

## Summary

The overarching message of this review is that PK variability is a significant problem for antifungal therapy in the treatment of invasive candidiasis in adult patients. While its impact on treatment outcome in the past may have been minimized by lower MICs, increasing resistance among the echinocandins and triazoles is now pushing the limits of conventional dosing (Table 2). Therefore, new dosing paradigms rooted in PK/PD principles, analogous to once-daily (infrequent) dosing of aminoglycosides or continuous infusions of  $\beta$ -lactams with possible TDM, should be explored for current and future antifungal agents to maximize their effectiveness and preserve their utility for future generations of patients who will be at risk of invasive candidiasis.

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