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*Published in:*
Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill

*DOI:*
10.1007/978-981-10-5336-8_11

# Chapter 11
# Antifungal PK/PD in the Critically Ill

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## 11.1 Introduction

Invasive fungal disease (IFD) can be life-threatening. In the past two decades, the incidence of these infections has increased significantly, largely because of the increasing number of patients at risk [1]. Although IFD can affect people with an intact immune systems as well, the vast majority of these infections occur as opportunistic infections in the immunocompromised host. IFD can be caused by both yeasts and filamentous molds. Yeasts are a type of fungi that consist of solitary cells that reproduce by budding, whereas molds occur in the form of hyphae: long, tubular branches with multiple, genetically identical nuclei which grow by apical extension. The most common forms of IFD in the immunocompromised host include invasive candidiasis (yeast) and invasive aspergillosis (mold).

## 11.2 Invasive Candidiasis

Yeasts such as *Candida* spp. are part of our normal microbial flora on mucosal surfaces (primarily the gut, the oral cavity, and the upper respiratory tract, although the skin may also provide a habitat), from where they may translocate into the tissues or blood in patients with varying underlying diseases or host factors, causing

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A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_11

invasive disease (invasive candidiasis), most often presenting as candidemia [2]. At a later stage, candidemia can undergo secondary dissemination to organs (e.g., eyes, liver, spleen, bones, heart valves, central nervous system) or present as deep-seated candidiasis [2, 3].

The pathogenesis of invasive candidiasis involves three major components: (a) increased fungal burden or colonization, mostly resulting from the use of broad-spectrum antibiotics; (b) disruption .of normal mucosal barriers induced by disease, drugs, trauma, or intravascular catheters; and (c) immune impairment (e.g., neutropenia) [4]. Not surprisingly, invasive candidiasis occurs most frequently in immunocompromised hosts and critically ill patients, with mortality rates reported to be as high as 40%, despite the use of antifungal therapy [2].

## 11.3 Invasive Aspergillosis

Molds such as *Aspergillus* spp. are saprophytic filamentous fungi and found widely in the environment. They are commonly found in both the outdoor and the indoor environment, including hospitals [5, 6]. Invasive aspergillosis, i.e., *Aspergillus hyphae* penetrating the lung tissue and entering the bloodstream via the distal airways and alveolar spaces of the lung [7], is a serious opportunistic infection that mainly affects immunocompromised patients, particularly patients with hematological malignancies (e.g., leukemia), solid-organ and hematopoietic stem cell transplant patients, patients on prolonged corticosteroid therapy, and patients suffering from genetic immunodeficiencies (e.g., chronic granulomatous disease) [8, 9]. In addition, prolonged critical illness is now considered an additional risk factor for invasive aspergillosis [10]. In these high-risk populations, mortality rates for invasive aspergillosis range from 40 to 90% [8, 11].

Other pathogens besides *Candida* spp. and *Aspergillus* spp. that cause IFD in the immunocompromised host are *Mucorales* spp. (zygomycosis), *Fusarium, Scedosporium* spp. (hyalohyphomycosis), *Pneumocystis*, and *Cryptococcus* spp. Although these infections are less common, specifically in the intensive care unit, they are associated with a high mortality rate.

## 11.4 Antifungal Drugs in Clinical Use

Based on their mode of action (Fig. 11.1), antifungal drugs frequently administered for systemic use have been grouped into four classes, namely, triazoles (fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole), echinocandins (anidulafungin, caspofungin, micafungin), polyenes (lipid complexes of amphotericin B), and fluoro-pyrimidines (flucytosine [5-FC]).

Triazoles act by targeted inhibition of the cytochrome (CYP) P450 dependent enzyme lanosterol demethylase, thereby interrupting the synthesis of ergosterol.

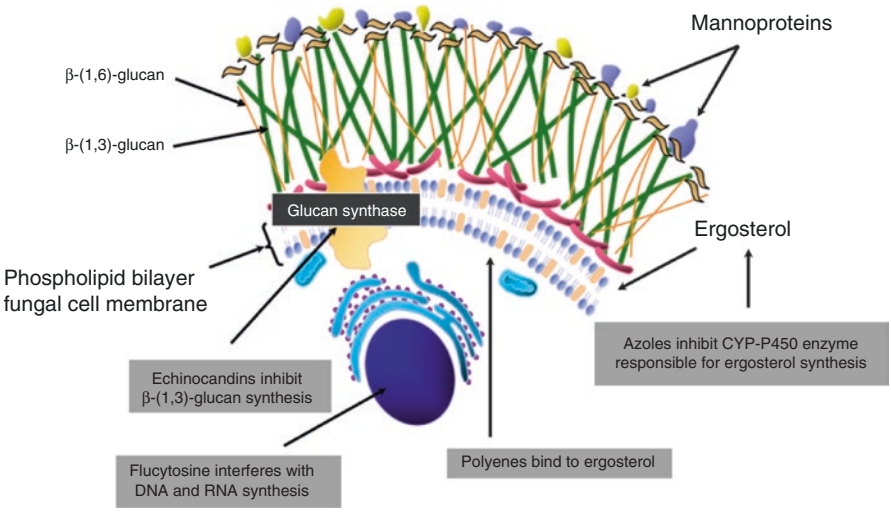


**Fig. 11.1** Schematic overview of current antifungal agents and their mechanism of action. Adapted from Kartsonis et al. [159]

This inhibition leads to depletion of ergosterol and the accumulation of sterol precursors in the fungal cell membrane, causing increased membrane permeability and inhibition of fungal growth [12]. Echinocandins act by noncompetitive inhibition of β-(1,3)-D-glucan synthase, thereby blocking the synthesis of this major component of the fungal cell wall. This compromises cellular structural integrity and morphology, ultimately resulting in osmotic lysis of the fungal cell [13].

Amphotericin B acts by binding directly to membrane sterols (especially ergosterol) in the fungal cell membrane. Through self-assembly of amphotericin B molecules, ionic transmembrane channels are formed that cause the fungal cell to leak its intracellular contents (e.g., potassium), subsequently leading to cell death [14].

The pyrimidine analog 5-FC itself has no intrinsic antifungal activity, but once it has been taken up by fungal cells, it is converted to 5-fluorouracil (5-FU). Metabolites of 5-FU act by inhibiting the DNA and RNA synthesis in the nucleus of the fungal cell [15].

## 11.5 Pharmacokinetics of Echinocandins in Critically Ill Patients

The pharmacokinetics (PK) of antifungal drugs, much like antimicrobials, can be highly variable in critically ill patients due to several physiological factors such as a hyperdynamic state, third spacing, hypoalbuminemia, renal dysfunction, hepatic dysfunction, and organ support [16, 17]. Furthermore, extracorporeal membrane oxygenation (ECMO) can alter the PK of drugs due to the addition of blood

products to the circuit and potential binding of drugs to the surface of the ECMO circuit [18]. The consequence of these changes in PK is that the echinocandins might present lower exposure in critically ill patients.

Echinocandins have been extensively studied in critically ill patients with the consequence that many issues around their altered PK in critical illness are now more thoroughly understood. There are, however, noticeable differences in PK between the three echinocandins including the need for loading doses of anidulafungin and caspofungin, the metabolic pathways (hepatic versus non-hepatic or a combination of both), and the number and extent of clinically relevant drug–drug interactions (see http://www.fungalpharmacology.org for an extensive overview of drug–drug interactions with echinocandins). There are no head-to-head comparative efficacy trials in critically ill patients and, at present, the three available echinocandins are considered equivalent. With such comparable guideline recommendations, apart from those in neonates and children, the PK differences are the only aspects that may support a specific choice (Table 11.1).

Anidulafungin is given as a 200 mg loading dose on day 1 followed by a 100 mg daily maintenance dose. PK in critically ill patients have been fairly well described for anidulafungin. Both comparable exposure in critically ill patients and reduced exposure (decreases in the area under the concentration time curve [AUC0–24] of 25% and trough concentrations [$C_{min}$] of 40%) [19–21] have been reported in reference to healthy volunteers. There is a general tendency to lower exposure of anidulafungin in critically ill patients, but up until today no major dominant factors associated with altered PK have been identified. Disease severity scores and albumin concentrations appear not to influence anidulafungin PK [19–21]. The pharmacodynamic goals of anidulafungin are not yet well defined and underdosing looms in critically ill patients.

Caspofungin is given as a 70 mg loading dose followed by a 50 mg maintenance dose. It is recommended to increase the maintenance dose to 70 mg if body weight exceeds 80 kg. Like anidulafungin, PK data for caspofungin in critically ill patients are conflicting. In surgical ICU patients, caspofungin $C_{min}$ plasma concentrations were slightly increased compared to healthy volunteers (2.16 mg/L vs. 1.41 mg/L) [22]. Another study in 20 ICU patients with (suspected) invasive candidiasis found lower exposure to caspofungin on day 3 compared to historical controls [23]. But in a marginally larger cohort of general ICU patients ($n = 27$), caspofungin AUC was comparable to healthy volunteers [24–26]. No factors that might influence the PK of caspofungin were identified, although the sample size might have been too low to detect significant covariates [24, 25].

Unlike anidulafungin and caspofungin, micafungin does not require a loading dose. From day 1 onwards, it is given as a single daily dose of 100 mg. Similar to caspofungin, the PK of micafungin has been extensively studied. Critical illness appears to impact the exposure to micafungin as ICU patients had lower exposure after standard dosages of micafungin compared to healthy controls. Unfortunately, this study did not identify any relevant covariates to explain the lower exposure, which was potentially caused by the limited number of patients ($n = 20$). In a second study in 100 patients, the micafungin clearance of 1.34 L/min was markedly higher than

**Table 11.1** Comparative pharmacokinetics of triazole and echinocandin antifungal agents in healthy volunteers [12, 154–158]

| PK parameter | Antifungal drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | FLZ | ITZ[a] | PSZ[b] | VCZ | ISA | ANF | CAS | MCF |
| Drug formulations | IV/C/S | IV[c]/C/S | IV/T/S | IV/T/S | IV/C | IV | IV | IV |
| *F* (%) | >90 | 50 | 54 | 96 | 98 | <5 | <5 | <5 |
| $AUC_{0-24}$ (mg*h/L) | 400–800 | 29.2 | 8.9 | 20.3 | 121.4 | 110 | 97.6 | 132.6 |
| $C_{max}$ (mg/L) | 6–20 | 0.5–2.3 | 1.5–2.2 | 3–4.6 | 7.5 | 7.2 | 12.1 | 8.8 |
| $T_{max}$ (h) | 1–2 | 2.2–2.5 | 4–5 | 1–2 | 3 | N/A | N/A | N/A |
| $V_D$ (L/kg) | 0.56–0.82 | ~11 | 7–25 | 4.6 | 4.4–7.7 | 0.6 | N/A | 0.25–0.27 |
| PPB (%) | 11–12 | 99.8 | 99 | 58 | >99 | 99 | 97 | >99 |
| CSF (%) | >60 | <10 | ND | 60 | Poor in CSF, good in brain[d] | <5 | <5 | <5 |
| Vitreous (%) | 28–75[d,e] | 10[d] | 26[d,e] | 38[d] | Good | 0[e] | 0[d] | <1[e] |
| Urine (%) | 90 | 1–10 | <2 | <2 | <1 | <2 | <2 | <2 |
| Metabolism | Minor hepatic | Hepatic (CYP3A4) | Minor Hepatic (UGT) | Hepatic (CYP2C19, 2C9, 3A4) | Hepatic (CYP3A4, UGT) | N/A (nonenzymatic degradation) | Hepatic (hydrolysis, N-acetylation) | Hepatic (arylsulfatase and catechol-O-methyltransferase) |
| Elimination | Renal | Hepatic | Feces | Renal | Feces | Feces | Urine | Feces |
| CL (L/h) | 0.27–0.63 | 22.9 | 32 | 20 | 2.6 | 0.96 | 0.63 | 0.63 |
| $T_{1/2}$ (h) | 30 | 24 | 25 | 6 (but nonlinear PK) | 130 | ~24 | 10.6 (β-phase) | 14.7 |

[a]Oral solution formulation
[b]Tablet formulation
[c]IV formulation not available in all countries
[d]Data from human studies
[e]Data from animal studies

reported in the literature, and higher than the study reported by Lempers et al. [27]. Body weight, albumin, and SOFA score were found to significantly influence the interindividual variability in clearance (CL), volume of the central compartment, and peripheral compartment. In general, the exposure of critically ill patients to micafungin is potentially lower than healthy controls and dosages should be adjusted upward.

## 11.6 Use of Echinocandins in Patients with Renal Impairment, Renal Replacement Therapy, and ECMO

Patients with varying stages of renal impairment showed no statistical differences in PK for anidulafungin and micafungin compared to matched healthy volunteers. Therefore, these echinocandins provide an excellent therapeutic option in patients with renal failure. The PK of anidulafungin 50 mg and micafungin 100 mg single dose was unaffected by renal impairment, as no significant differences in AUC, peak concentration ($C_{max}$), CL, volume of distribution (Vd), or half-life were observed compared to healthy volunteers [28, 29]. Contrary to anidulafungin and micafungin, there are no publications on PK of caspofungin in patients with renal failure. The scarce information that is available on caspofungin is derived from the medicines authorities [30]. Increases in exposure to caspofungin were seen in patients with different degrees of renal impairment (increases in AUC of 31%, 49%, and 30% in patients with moderate, severe, and end-stage renal disease, respectively). Whether these higher exposures lead to either toxicity or improved pharmacodynamics in critically ill patients needs to be investigated.

In the ICU, when native renal function deteriorates precipitously, continuous renal replacement therapy (CRRT) is typically provided. Continuous exposure to extracorporeal devices (e.g., tubing, catheters, filters) might profoundly alter the PK of echinocandins. In this fashion, the PK of anidulafungin in patients dependent on chronic intermittent hemodialysis were comparable to healthy volunteers and were not influenced by the time of drug administration in relation to the time of dialysis. Furthermore, no anidulafungin concentrations were found in dialysate [29]. Extended daily dialysis (8 h) did not change PK of anidulafungin, and no measurable anidulafungin concentrations were found in the dialysate [31].

Like in intermittent hemodialysis, anidulafungin PK in critically ill patients undergoing CRRT were comparable to PK in healthy volunteers, and patients with a fungal infection. No accumulation of anidulafungin was seen within 3 days of treatment [32, 33]. Similarly effluent samples did not contain measurable levels of anidulafungin [32, 33]. Therefore, at present, there is no adjustment of anidulafungin advised for patients on CRRT.

The PK parameters of caspofungin after a single dose and multiple doses during CRRT in critically ill patients were, like anidulafungin, unchanged [26, 34]. Small differences in pre-filter and post-filter concentrations suggest that there might be some adsorption of caspofungin to the hemofilter membranes, but caspofungin PK parameters were not significantly influenced [26].

In critically ill patients undergoing CRRT, the PK of micafungin was similarly unaffected [35, 36]. During CRRT, plasma samples from the inlet and outlet of the extracorporeal circuit were comparable and no micafungin was detected in effluent [35]. No adsorption to or saturation of the polysulfone and polyethersulfone filters was reported [36].

Data on caspofungin PK in patients on ECMO therapy is limited and provides varying results. Plasma concentrations of caspofungin in surgical ICU patients varied between undetectable or low (1.8 and 3.4 mg/L; single patient two occasions) and normal concentrations in comparison to healthy volunteers [18, 37]. Anidulafungin has been applied to critically ill patients while on ECMO. Anidulafungin concentrations were not influenced by the oxygenator or tubing [38]. Research in adult patients on ECMO receiving micafungin is lacking. Micafungin was evaluated in pediatric patients on ECMO and the Vd and CL were at the upper limits of normal in comparison to patients not on ECMO [39].

## 11.7 Use of Echinocandins in Patients with Hepatic Insufficiency

No significant changes in the PK of anidulafungin are observed in patients with mild and moderate hepatic impairment when compared to healthy volunteers [29]. However, patients with severe hepatic impairment show significantly decreased AUC and $C_{max}$ values compared to healthy volunteers [29]. AUC and $C_{max}$ are decreased by 33% and 36%, respectively. CL and Vd are increased by 57% and 78%, respectively, but were not considered clinically relevant by the authors. The most likely explanation for this lower exposure is an increase in Vd caused by ascites and edema [29]. However, in a single severely hepatic impaired patient requiring albumin dialysis, anidulafungin PK did not appear to be affected [40].

For caspofungin, the AUC0-∞ is increased by 55 and 76% in patients with mild and moderate hepatic impairment, respectively. In addition, the $C_{min}$ and elimination half-life are increased as well in comparison to healthy volunteers [41]. After multiple dose administration of caspofungin (70 mg loading dose, followed by 35 mg OD), moderate PK changes were observed in mild hepatic impairment, but these changes were not considered clinically relevant [41]. More specifically, on days 1, 7, and 14 AUC0–24 increased by 17%, 26%, and 21%, respectively; whereas on days 1, 7, and 14 $C_{min}$ increased with 50%, 70%, and 44%, respectively. Multiple dose administration of caspofungin (70 mg loading dose followed by 35 mg OD) to patients with moderate hepatic impairment showed no significant differences in AUC0–24 on days 7 and 14 as compared to healthy volunteers receiving the standard dose; $C_{max}$ and $C_{min}$ were decreased by 20% and 23% and by 71% and 50% on days 7 and 14, respectively [41]. A maintenance dose reduction to 35 mg OD in patients with moderate or severe hepatic impairment, as classified by Child Pugh score, is advised as caspofungin PK is affected by the degree of hepatic impairment [30, 41]. Even though the patient populations in these registration studies were

small (6–8 patients for each degree of hepatic impairment), these results were the rationale for dose adjustment in patients with moderate and severe hepatic impairment. The differences in caspofungin PK in hepatically impaired patients are possibly due to decreased clearance mediated by the uptake transporter OATP1B1 in hepatocytes [41]. In contrast, case reports and cohort studies with critically ill patients with mild to moderate hepatic impairment treated with caspofungin 70 mg OD or 50 mg OD showed that dose reductions to 35 mg would possibly have led to suboptimal exposure of caspofungin [24, 42–44].

Pediatric patients with hepatic impairment, similar to adult patients, demonstrate high variability of caspofungin exposure; PK parameters after a daily dose of 1 mg/kg range from being comparable to adult patients to less than half of those seen in adults (AUC0–24 40–50% $C_{max}$ 50% and $C_{min}$ 60% of adult values) in combination with significant increases in CL and Vd (155% and 218%, respectively) [45].

Micafungin exposure in patients with moderate and severe hepatic impairment is decreased in comparison to healthy volunteers (98 mg h/L in patients with moderate hepatic impairment versus 126 mg h/L in healthy volunteers and 100 mg h/L in patients with severe hepatic impairment versus that of 142 mg h/L in healthy volunteers, respectively) [28, 46]. There is no change in the unbound fraction of micafungin in patients with both moderate and severe hepatic impairment compared to healthy volunteers. Interestingly, patients with severe hepatic impairment have higher plasma concentrations of the M5 metabolite, compared to healthy volunteers, possibly due to reduced clearance of the M5 metabolite (the activity of the M5 metabolite is estimated to be only 1/125th of the parent compound) [46]. For patients with both moderate and severe hepatic impairment, the differences in exposure were not considered to be clinically relevant, as a consequence no dose adjustments are advised for patients with any grade of hepatic impairment [28, 46]. In accordance, in living donor liver transplant recipients, micafungin PK was comparable to healthy subjects [47–49].

## 11.8 Clinical Pharmacology of Echinocandin Drugs

Only very few studies have investigated the relationship between PK and efficacy or toxicity. For echinocandins, the AUC to minimum inhibitory concentration (fAUC:MIC) ratio (using free drug concentration) is the index linking PK to PD [50–53]. Much like other antimicrobial agents, target concentrations have only been defined in animal models or from a single analysis from phase II/III studies. These targets must be defined prior to installing a personalized treatment approach using therapeutic drug monitoring.

Once these target concentrations are established, they will allow Monte Carlo simulations to determine the probability of target attainment (PTA) with specific dosing regimes in critically ill patients [24, 27, 50–52, 54].

Echinocandins are generally administered as a fixed dose (with or without a loading dose) and partly adjusted for body weight. Mixed results have been noted in several smaller PK studies showing lower but also normal concentrations in critically

ill patients compared to non-critically ill patients. Clinical studies that correlate exposure with outcome are urgently needed to be able to make definitive recommendations on using TDM with echinocandins [20, 21, 23, 24, 55, 56].

For caspofungin, no clinical target concentrations have been identified. A limitation of the PTA analysis with caspofungin is thus the absence of a human PK/PD target. A preclinical target derived from a neutropenic mouse model has been used instead [50, 57]. Future studies are warranted to identify the human fAUC:MIC ratio of caspofungin associated with better treatment outcomes. This may be performed similar to a previous analysis on the micafungin PK/PD target as proposed by Andes et al., in which a large group of patients were evaluated on both PK, susceptibility pattern of the pathogen and clinical outcome [58]. Their statistical analysis yielded the most probable fAUC:MIC value associated with mycological response based on two phase 2/3 studies. Even this analysis had some limitations. For instance, "mycological response" was used for treatment outcome. Mycological cure was based on "periodic" or weekly mycology laboratory assessment. It is questionable whether weekly mycology assessment is frequent enough. Moreover, in cases of missing information on micafungin exposure, they used population values, despite high variability between individual predictions and population predictions (precision was about 20%). Such an approach is challenging, as demonstrated by Liu et al. [19], where they could not identify a solid fAUC/MIC target for anidulafungin, using "mycological cure endpoint" data from phase 2/3 studies. Alternative approaches must be found to derive these crucial targets to guide therapy.

An alternative to direct clinical outcome measures such as "mycological cure" or "survival" might be the use of surrogate parameters such as B-glucan. Currently, this biomarker is a promising early diagnostic screening tool for invasive fungal infections, but its role in PK/PD target identification and PD assessment remains to be explored. It may prove beneficial to link B-glucan as a PD endpoint to drug concentrations.

## 11.9 Pharmacokinetics of Azole Drugs in Critically Ill Patients

Currently, three azole antifungal drugs are frequently used in the intensive care unit, fluconazole, voriconazole, and posaconazole. The use of itraconazole is very limited due to the lack of an intravenous formulation in many countries. Isavuconazole has recently entered the market but data on PK in critically ill patients are lacking as well as PK/PD analyses of isavuconazole in this cohort.

Fluconazole, posaconazole, and voriconazole show markedly different PK behavior in both healthy volunteers but specifically in critically ill patients. These differences between the three azole drugs can be explained by extent of protein binding, the metabolic pathways involved in degradation (including variability due to genetic mutations), renal clearance, and drug–drug interactions [59–62]. Clearly, the variability in clinical condition of the critically ill patient will likely influence the PK of azole drugs [16].

The number of papers on voriconazole PK in critically ill patients is very limited and most of the evidence comes from hematological patients [63–66]. Despite the lack of intensive PK studies in this population, some similarities with other populations may be expected. Voriconazole PK is highly variable in all populations due to age, liver function, polymorphisms in drug metabolizing enzymes, and drug–drug interactions [59]. Recently, an association between clearance of voriconazole and inflammation was suggested. The authors demonstrated that higher voriconazole concentrations were associated with increased C-reactive protein concentrations [67]. Although voriconazole is not extensively bound to plasma proteins, a multivariate analysis revealed a significant relationship with plasma protein binding and plasma albumin concentrations ($P < 0.001$), demonstrating higher unbound voriconazole concentrations with decreasing albumin levels. Of note, the correlation is more pronounced in the presence of elevated bilirubin concentrations [68]. Measurement of the unbound voriconazole concentration may help to detect toxic unbound drug concentrations, even when the total drug concentration is within the therapeutic range [68, 69]. The nonlinear behavior of voriconazole makes it difficult to predict the plasma drug concentration and TDM has therefore been recommended [63] (Table 11.2).

The number of publications on posaconazole PK in critically ill patients is even less abundant than voriconazole [70]. Posaconazole is a highly protein bound, lipophilic drug with a very large Vd. This azole was only available as an oral suspension until 2015, but has since been manufactured as a solid oral formulation (tablet), as well as an intravenous solution. Posaconazole oral solution demonstrated a large interindividual and intraindividual variation in bioavailability as pH and food affected the absorption of the drug [71–73]. Moreover, administration by nasogastric tube of this formulation further reduced the bioavailability [74]. The use of posaconazole oral solution in critically ill patients had substantial drawbacks [70]. Data on the new solid oral formulation and the intravenous formulation in critically ill patients is completely lacking. Since posaconazole is highly protein bound (98%), changes in the unbound fraction in patients with hypoalbuminemia should be considered when interpreting measured total concentrations.

Several studies have been performed with fluconazole in critically ill patients. Buijk et al., Nicolau et al., and Rosemurgy et al. performed studies to determine the bioavailability of enteral fluconazole compared to intravenous fluconazole in relatively small

**Table 11.2** Contemporary target drug concentrations for voriconazole and posaconazole when used in critically ill patients

| Triazole | Efficacy target (mg/L) | Toxicity target (mg/L) | Timing of first trough sample |
|---|---|---|---|
| Voriconazole | >1–2 | <5–6 | After 2–5 days |
| Prophylaxis Therapy | >1–2 | <5–6 | (Repeat sampling recommended) |
| Posaconazole | >0.7 | No recommend | Tablet/IV: after 3-5 days |
| Prophylaxis Therapy | >1.0 | No recommend | 3 days: Suspension: 5–7 days* |

*means that the use of posaconazole suspension is discouraged and that the oral tablet is prefered due to the favourable absorption profile

patient populations ($n$ = 5–14 patients). All showed an increase in Vd compared to healthy volunteers. In addition, bioavailability showed significant intrapatient variability [75–78]. However, results concerning CL and half-life were conflicting. Nicolau et al. and Rosemurgy et al. showed an increase in CL, but no effect on half-life compared to healthy volunteers, while others showed an increase in half-life without an increase in CL compared to healthy volunteers [75, 76]. Fluconazole was also studied in the multinational study on defining antibiotic levels in the intensive care (DALI) and again showed a large interindividual variability with about a third of the patients not reaching a therapeutic target concentration [56]. Aoyama and colleagues studied covariates that might influence the PK of fluconazole, and found creatinine clearance and body weight to key determinants of CL and Vd, respectively [79].

## 11.10 Use of Azole Drugs in Patients with Renal Impairment, Renal Replacement Therapy, and ECMO

It is well known that significant differences exist between the azole drugs with respect to protein binding and renal clearance. This determines whether dosages have to be adjusted in patients with deteriorating renal function or in patients already on supportive treatment like CRRT or ECMO.

Voriconazole at the licensed dose resulted in highly variable drug concentrations in critically ill patients [66]. Despite high interindividual variability in voriconazole concentrations, none of the patients experienced deterioration in renal function. Several studies have been performed investigating the effect of CRRT on voriconazole CL, which was not significant altered. Results were consistent between studies and standard dosages of voriconazole can be used without dose adjustment in patients undergoing CRRT. However, as described earlier, since the voriconazole concentration itself was highly variable, monitoring seems required.

In addition, the excipient sulfobutylether-β-cyclodextrin (SBECD) present in the parenteral formulation of voriconazole accumulates with renal impairment, and therefore intravenous administration of voriconazole to a patient with an estimated glomerular filtration rate below 50 mL/min is discouraged by the manufacturer [80]. However, critically ill patients often have impaired renal function and require IV administration because oral administration is complicated by gastroparesis or malabsorption. Therefore several studies have investigated the PK of SBECD and demonstrated it can be safely administered without a further decline in renal function [81–84]. In addition, CRRT effectively removed SBECD without a significant risk accumulation. Intermittent hemodialysis was able to effectively eliminate SBECD, but could not prevent a certain degree of accumulation [81, 85, 86]. Although the total number of studied subjects was low to make definite safety recommendations, toxicity due to SBECD was not observed.

Being a lipophilic drug, voriconazole showed significant sequestration in the ECMO circuit (Mehta et al. reported a 71% loss of voriconazole), necessitating higher doses of the drug to maintain adequate trough concentrations [87]. If this

initial loss is not compensated for, voriconazole levels will be subtherapeutic. However, later, when the circuit is saturated, voriconazole can accumulate and toxicity has been observed by several groups [18, 37, 88]. Confirmation of these findings are needed. In such a scenario, TDM may be helpful in optimizing voriconazole concentrations.

Posaconazole PK was studied in subjects with varying degrees of renal impairment including dialysis. No correlation was observed between posaconazole clearance and mild to moderate renal disease. In addition, posaconazole clearance was unaffected by dialysis which could be explained by the high protein binding (>98%). Dose adjustments were therefore not considered relevant.

Approximately 80% of fluconazole is eliminated unchanged via the kidneys. Renal function therefore impacts the PK of fluconazole; half-life is increased from 30 to 96 h in patients with a GFR <20 mL/min [89]. As such, the product information of fluconazole advises dose adjustments for patients with a GFR ≤50 mL/min [90]. Unfortunately, patients with impaired renal function (and impaired hepatic function) were excluded from studies on fluconazole PK by Buijk et al., Nicolau et al., and Rosemurgy et al. [75–77], such that the PK parameters in renally impaired ICU patients are lacking. As such, dose reductions are recommended in patients with renal insufficiency after the standard loading dose is administrated. However, cut-off values for renal function range from a GFR 10–50 mL/min. Once renal replacement therapy is indicated, the dose has to be increased again because clearance of fluconazole by CRRT is significant [91–94]. A daily dose of 800 mg may be required to reach therapeutic concentrations, and should be guided by monitoring of drug concentrations.

Fluconazole was not affected by ECMO as shown in an ex-vivo circuit [95]. However, in children, it was shown that it took much longer to reach comparable concentrations compared to children not on ECMO [96, 97]. Clearly, the additional volume had a more distinct effect in children than in adults. Watt et al. recommend a fluconazole loading dose of 25 mg/kg to overcome this problem [96, 97].

## 11.11 Use of Azole Drugs in Patients with Hepatic Insufficiency

Voriconazole is extensively metabolized by cytochrome P450 enzymes (2C19, 3A4, and 2C9). It is recommended to maintain the loading dose but to reduce the maintenance dose by 50% for Child-Pugh A and B cirrhosis [80]. In this context, the half-life of voriconazole is extended in patients with hepatic impairment [98]. Furthermore, higher voriconazole concentrations have been associated with a deterioration in liver function tests, but a clear cut-off concentration has not been established [99]. A concentration above 4 mg/L has been proposed as a risk factor for hepatotoxicity [100].

In a single dose study of posaconazole in patients with hepatic impairment, no clear difference was observed in drug exposure between different groups [101]. In a pooled analysis, a modest increase in exposure was observed in subjects with

impaired hepatic function compared to healthy volunteers. Although there is no clear need to adjust the dose in patients with hepatic impairment, TDM may be used to assure that toxic concentrations are not occurring.

In patients with mild to moderate hepatic impairment, no statistically significant effect on fluconazole PK parameters was observed [102]. This can be explained by predominant renal excretion of the unchanged compound.

## 11.12 Clinical Pharmacology of Azole Drugs

In general, drugs used for life-threatening diseases with a proven PK/PD relationship, narrow therapeutic range, large interindividual variation in PK, and severe adverse effects are particularly good candidates for TDM [103, 104]. In this fashion, PK/PD relationships need to be well defined. In the clinical setting, there are observational data suggesting that achieving plasma concentrations above a certain threshold may confer greater efficacy for voriconazole, posaconazole, and itraconazole [15, 105–111], although this has yet to be shown in prospective trials.

It should be noted that robust data on PK/PD relationships in critically ill patients are currently lacking. Most of the evidence collected is from hematology patients. Thus extrapolations from this population to the ICU population must be made. This should be done with caution as the course of disease, immune response, and drug behavior will be different in ICU patients compared to hematology patients.

The importance of TDM for these antifungals is acknowledged, although trials to evaluate this practice have not been performed, and data are not yet conclusive enough to support its routine use [108].

### *11.12.1 Voriconazole*

It has been widely reported in the literature that the PK/PD index for triazole antifungal drugs is the AUC/MIC ratio [112–114]. Trough concentrations correlate well with AUC [109, 115] and are therefore used as surrogate markers for total exposure. Several retrospective studies have identified a relationship between voriconazole trough concentrations and clinical outcomes during prophylaxis or treatment [116–118]. Moreover, several prospective clinical trials have demonstrated an association between plasma trough concentrations and efficacy and toxicity during treatment of invasive fungal infections, whereas others had too few patients [105, 119–123]. New research points us towards a possible role for galactomannan as it appears to be a very elegant surrogate marker that can help guide therapy [124, 125].

Both retrospective and prospective clinical studies have shown that trough concentrations $\geq$1.0–2.0 mg/L were associated with optimal clinical response in treatment of invasive fungal infections [108, 121, 123]. A prospective clinical trial validated the breakpoint of voriconazole and demonstrated the added value of TDM

during voriconazole treatment, by demonstrating a more favorable response in the TDM group, compared to the non-TDM group [108]. Furthermore, a retrospective study suggested that patients receiving prophylactic therapy with voriconazole concentrations >2 mg/L had a lower risk of obtaining an invasive fungal infection [117].

There is lively discussion on the relationship between voriconazole trough concentrations and the risk of toxicity. Trough concentrations ≥4.5–6 mg/L have been associated with a higher risk of voriconazole-associated neurotoxicity (visual and auditory hallucinations, encephalopathy) but the relationship with liver dysfunction is not as clear [99, 119, 123]. No reliable upper "cut-off" concentration can be identified to minimize risk of hepatotoxic effects with the possible exception of Japanese patients where hepatotoxicity was more common if voriconazole trough concentrations ≥3.9 mg/L [126, 127].

In summary, TDM is advised during treatment and also prophylaxis in critically ill patients prescribed voriconazole. Trough samples should be taken after about 2 days, and a range of 2–6 mg/L should be used as a reference.

### *11.12.2 Posaconazole*

For posaconazole, evidence is accumulating as to the benefits of TDM [107, 128–130]. The likelihood of encountering low exposure was typically seen with the older pharmaceutical formulation (suspension) [72]. With the development of the new solid oral tablet formulation, as well as the intravenous formulation, new debate has arisen on the benefits of TDM, as erratic absorption seems less of a problem and most patients will attain target concentrations [131–133]. One of the most important recommendations is therefore to use these new formulations to ascertain that high exposure is achieved specifically for the ICU patient. The downside of higher exposure is obviously the increased probability of encountering side effects. Concentration-dependent side effects of posaconazole include liver function test abnormalities, QT prolongation, and electrolyte disturbances.

Data on posaconazole TDM in critical illness are absent, and one must rely on that from hematology patients. Several clinical studies have reported a concentration–response relationship between posaconazole plasma trough concentrations and the risk of breakthrough infections, where $C_{min} > 0.7$ mg/L is suggested to result in optimal prophylactic efficacy [107, 130, 134–137]. For the treatment of invasive aspergillosis, a target trough concentration of >1 mg/L is suggested [128]. There is no upper limit for posaconazole exposure defined as yet, although the scientific discussion at the European Medicines Agency points towards an upper target of 3.75 mg/L [European Medicine Agency. Assessment report: Noxafil. 2014. Available at: http://www.ema.europa.eu/ema/]. There are unfortunately no clinical published data to substantiate this target.

The first assessment of trough concentrations is generally recommended on day 5. In the prophylactic setting, this is acceptable but in the setting of treatment this might be too late. Specific algorithms are proposed in literature to interpret earlier samples using nomograms [107, 138].

### *11.12.3 Fluconazole*

In general, TDM of fluconazole is not required as long as current dose recommendations are followed and renal function is closely monitored. However, in critically ill patients, stable conditions are seldom and situations may arise in which the measurement of fluconazole concentration can be highly informative. Augmented renal clearance, administration of high volumes of fluids, or infections in sanctuary sites may prevent reaching therapeutic targets in situations with higher MIC values and may require TDM. Moreover, the place of fluconazole to treat *Candida* infections in children is still substantial and TDM may be of added value [139]. As fluconazole is often included in multi-analyte antifungal assays and the information can be critical in specific situations, one should always consider obtaining these levels [140].

Based on the variation in absorption, bioavailability, Vd, and drug–drug interactions, the predictability of fluconazole concentration in critically ill patients is questionable. TDM on a regular basis (e.g., twice weekly) is strongly advised. Trough levels of 25–50 mg/L are associated with an adequate AUC:MIC, although proper dose-outcome studies in critically ill patients still need to be performed.

Finally, reports have emerged on resistance of *Aspergillus* to azole drugs, particularly in the setting of critically ill patients [141–145]. One must keep in mind that the presented breakpoints are valid for susceptible *Aspergillus* spp. But higher concentrations may be needed when a patient is infected with a species with a higher MIC [115]. Specific guidance on the management of disease caused by azole-resistant species has recently been published and can be used a starting point for treatment [146].

## 11.13 Pharmacokinetics of Liposomal Amphotericin B in Critically Ill Patients

Conventional amphotericin B deoxycholate has historically been considered the "gold standard" in the treatment of invasive fungal infections, although it has largely been abandoned in modern practice. In order to attenuate its toxicity and increase the therapeutic potential, alternative formulations of amphotericin B have been developed. The molecular structure of amphotericin B deoxycholate makes the drug an ideal candidate for incorporation into lipid-based preparations. The use of lipid formulations is associated with good fungicidal activity, low emergence of resistance and specifically fewer adverse effects, in particular nephrotoxicity, with no difference in efficacy. Liposomal amphotericin B (AmBisome) is an intravenous liposomal formulation that differs from other lipid-associated amphotericin B products in its uniform, small, spherical size, and the fact that it is a stable, lyophilized product. These liposomes are small unilamellar vesicles composed of molecules of amphotericin B intercalated into a phospholipid bilayer. The diameter of these liposomes is less than 100 nm. Liposomes provide a unique delivery system, which enhances delivery to fungal cells while reducing drug-associated toxicities.

Liposomal amphotericin B has a broad spectrum of activity, including against *Candida* species (with the exception of *Candida lusitaniae* and *Candida guilliermondii)*, Mucor species, *Aspergillus* spp. (with reduced efficacy against *Aspergillus flavus* and *Aspergillus terreus*), and *Cryptococcus* spp. The development of resistance to amphotericin B is rare.

## 11.14 General Pharmacokinetics of Liposomal Amphotericin B in ICU Patients

Despite the fact that liposomal amphotericin B has been licensed and marketed for many years, the PK of this drug is poorly understood. Multiple PK analyses studying a wide variety of dosages have been conducted in immunocompromised (pediatric) patients [147], although ICU patients are underrepresented. A study in critically ill patients gave liposomal amphotericin B at doses ranging from 1.2 to 4.2 mg/kg [148]. There was considerable variability in exposure in the 10 patients that received the most commonly used dosages (2.8–3.0 mg/kg). The apparent Vd was comparatively small with a median value of 0.42 liters/kg, and the median terminal elimination half-life was 13.05 h (range 8.7–41.4 h). There was no correlation, also in the other dosage groups, between dose and exposure nor between dose and $C_{max}$. These data corroborate with the data from previous studies with regard to large intra- and intersubject variability. $C_{max}$ concentrations in ICU patients were comparable to those reported in other groups of patients with similar dosages [149–152].

Yet, differences were also noted. For instance, in 17 hematology patients receiving dosages ranging from 2.67 to 3.46 mg/kg (average 3.0 mg/kg) [147], the terminal half-life of 54.3 h was substantially longer in this cohort than in the ICU population. The authors argued that the observed difference in half-life might be due to differences in the uptake of the liposomal carrier with bound drug into non-blood compartments or in the dissolution of the drug from the liposomal carriers with consequences for its disposition in the blood; additional potential factors include differences in disease status and inflammatory molecules, the composition of plasma proteins, and solutions used for concomitant parenteral nutrition.

## 11.15 Use of Liposomal Amphotericin B in Patients with Renal Impairment, Renal Replacement Therapy, and ECMO

As PK information on liposomal amphotericin B is scarce, robust data on drug handling in patients with deteriorating renal function or while receiving extracorporeal support is even more limited. According to the product information and the renal drug handbook [available via https://kdpnet.kdp.louisville.edu/drugbook/adult/], no dose adjustment is needed for patients with renal failure.

A previously reported study in critically ill patients had a subpopulation of patients also receiving hemodialysis. It appears that liposomal amphotericin B is not removed by this modality, but more data are needed to confirm this in a larger cohort of patients and other forms of dialysis [148]. At present, there are no publications on the PK of various formulations of amphotericin B and ECMO. Given the fact that all formulations of amphotericin B are lipophilic, adsorption to the ECMO tubing can be expected.

## 11.16 Use of Liposomal Amphotericin B in Patients with Hepatic Insufficiency

Hepatic side effects of liposomal amphotericin B have been reported in literature and these side effects are also listed in the product information. However, it is unknown whether changes in hepatic function have an impact on the clearance of liposomal amphotericin B. No formal recommendations are given for dose adaptations of liposomal amphotericin B in patients with varying degrees of hepatic impairment.

## 11.17 Clinical Pharmacology of Amphotericin B

A relationship between the PK profile of liposomal amphotericin B and its antifungal effect has been demonstrated in several in vitro studies but no study has been conducted to validate an optimal PK/PD index for liposomal amphotericin B in humans. In a population-PK analysis in nine patients with proven fungal infection, eight patients treated with liposomal amphotericin B manifest a clinical response (either complete or partial). In patients with a complete response, the steady-state $C_{max}$/MIC ratio was significantly higher than in patients with a partial response ($P = 0.021$), while no significant correlation was found between AUC/MIC and response [153]. Obviously, this study is not powered to derive a final breakpoint and only guides us towards the fact that based on these data it appears that exposure (especially $C_{max}$) to liposomal amphotericin B is the intermediate link between the doses administered and their clinical effects.

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