Antifungal PK/PD Considerations in Fungal Pulmonary Infections

Alexander J. Lepak, M.D.¹,² and David R. Andes, M.D.¹,²

ABSTRACT

Pharmacokinetic/pharmacodynamic (PK/PD) studies examine the relationships of drug pharmacokinetic properties, in vitro drug potency, and treatment efficacy. Study results are integral to the design of optimal dosing strategies, prevention of toxicity, development and interpretation of susceptibility break points, and prevention and recognition of drug resistance. These principles are increasingly utilized to optimize therapy for pulmonary fungal pathogens such as Aspergillus species, although they have been underutilized for other difficult-to-treat fungal pathogens. Understanding the design and implementation of PK/PD studies facilitates more effective utilization of the available antifungal agents to improve outcomes for many of these life-threatening infections.

KEYWORDS: Pharmacokinetics, pharmacodynamics, antifungal, Aspergillus, pulmonary

A number of factors impact the choice of an antifungal and drug-dosing regimen. Among these factors, spectrum of activity against the infecting pathogen and adequate accumulation of drug at the site of infection are critical for optimizing therapy. The field of study that considers these components of antimicrobial drug therapy is pharmacokinetics and pharmacodynamics (PK/PD).

Pharmacokinetic studies investigate how the body interacts with the drug, including absorption, distribution to the site of infection, metabolism, and elimination. Pharmacodynamics links drug concentration at the infection site to treatment outcome. An additional useful element of antimicrobial pharmacodynamic studies is consideration of a measure of in vitro drug potency or susceptibility, the minimum inhibitory concentration (MIC).

The PK/PD area of study has played an integral role in designing optimal treatment strategies for a number of infectious diseases.¹⁻⁴ These approaches allow caregivers to choose the most efficacious drug, determine the optimal dose and dosing frequency, define and recognize drug resistance, and interpret susceptibility testing. Application of PK/PD methods to the antifungal field has been focused predominantly on disseminated infection with Candida species. However, recent investigations have begun to apply these approaches to pathogens that afflict the lungs, particularly Aspergillus species.

The emergence of PK/PD studies for these pulmonary fungal infections is timely because treatment outcomes remain suboptimal despite the development of new antifungal drugs such as triazoles with potent Aspergillus activity and the addition of the echinocandin class. Investigators hypothesize that understanding antifungal pharmacokinetics and pharmacodynamic relationships for these pathogens offers an opportunity to enhance outcomes with the drugs that are currently

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available. This review considers antifungal PK/PD of pulmonary fungal infections with a focus on invasive pulmonary aspergillosis (IPA).

**DRUG CHOICE: SPECTRUM OF ACTIVITY**

Common fungal infections of the lower respiratory tract include *Aspergillus* species, organisms from the Mucorales order, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Penicillium marneffei*, and emerging pathogens such as *Fusarium* species, *Scedosporium apiospermum*, *Scedosporium prolificans*, and agents that cause phaeohyphomycosis (dark-pigmented molds). A comprehensive review of the therapeutic choices and selection process for each of these infectious agents is included in this topical volume and is outside the scope of this review article. However, this article briefly describes the spectrum of activity and in vitro susceptibility or potency in the context of PK/PD analyses. Of all systemic antifungal agents, amphotericin B (AmB) and its lipid congeners have the broadest spectrum and potent activity against all of the aforementioned pathogens except *A. terreus*, *S. apiospermum*, and *S. prolificans*. There is also limited effectiveness against many of the agents that cause phaeohyphomycosis.

The systemic triazoles include itraconazole, fluconazole, voriconazole, and posaconazole. Each exhibits both common and unique antimicrobial properties. Itraconazole, the first of the available systemic triazole agents, has broad in vitro activity against *Aspergillus* spp., *C. neoformans*, *B. dermatitidis*, *H. capsulatum*, *C. immitis*, *P. brasiliensis*, *S. schenckii*, *Penicillium* spp., and many of the agents of phaeohyphomycosis. The next triazole agent available for clinical use was fluconazole. The spectrum, in terms of fungal pulmonary pathogens, is limited to *C. neoformans*, *H. capsulatum*, *B. dermatitidis*, *S. schenckii*, *C. immitis*, and *P. brasiliensis*. With the exception of cryptococcosis, the in vitro potency of fluconazole is lower than that of the other available triazoles. Voriconazole has broad activity for pulmonary fungal pathogens. U.S. Food and Drug Administration (FDA)-approved indications include pulmonary *Aspergillus* infections (for which it is considered first-line therapy), *S. apiospermum*, and *Fusarium* species. Its spectrum also includes *B. dermatitidis*, *H. capsulatum*, *C. immitis*, *P. brasiliensis*, *S. prolificans*, *C. neoformans*, and *P. marneffei*. Voriconazole is not effective against mucormycosis. The most recently available triazole agent, posaconazole, has a spectrum similar to voriconazole with the addition of the Mucorales order. The echinocandin class represents the most recently developed drug class. The spectrum of activity against pathogens producing fungal pulmonary infections is limited to *Aspergillus* species.

**Antifungal Pharmacokinetics**

Select antifungal pharmacokinetic properties are presented in Table 1. Despite the fact that amphotericin B is the first available antifungal, much detail regarding pharmacokinetics are not available. Clinically relevant information regarding this important drug includes the lack of impact of either renal or hepatic organ dysfunction on pharmacokinetics. Thus, whereas the dose-limiting toxicity is predominantly nephrotoxicity, dose reductions are unlikely to produce sufficient infection site concentrations. Among the lipid formulations there are marked differences in kinetic profiles. Liposomal amphotericin B produces the highest serum and CSF concentrations. The relevance of the latter has been associated with enhanced efficacy compared to the other formulations in a fungal infection model. Groll and colleagues examined the relationship between CSF and brain kinetics of each of the AmB preparations and efficacy. The CSF concentrations of four polyene compounds were remarkably similar. Brain tissue concentrations of liposomal AmB, however, were from six- to 10-fold higher than the other polyene preparations. The burden of *Candida* in the brains of rabbits following therapy correlated well with brain tissue penetration of the various drugs. This concept may be relevant for treatment of pulmonary fungal infections that disseminate to the CNS.

Among the AmB formulations, the lipid complex formulation has been shown to produce higher ELF concentrations, much of which can be accounted for by intracellular accumulation in alveolar macrophages. Animal model study of pulmonary aspergillosis linked

**DRUG CHOICE: PHARMACOKINETIC PRINCIPLES**

The study of pharmacokinetics (PK) involves understanding the interaction of a drug with the host, including measurements of absorption, distribution, metabolism, and elimination. From an antiinfective perspective, PK studies therefore determine the extent of drug penetration into the site of infection. Antifungal drug concentrations have been well characterized in serum, urine, cerebrospinal fluid (CSF), vitreous body, epithelial lining fluid (ELF), brain, lung, and kidney. However, the majority of fungal disease is in extracellular tissue fluid. Therefore, serum is an excellent surrogate for the extravascular tissue site concentration. The central nervous system (CNS) and ocular infection sites represent clear exceptions to this rule. Recent study with antibacterial drugs suggests the importance of a lung compartment termed the ELF. This fluid is the infection site for most extracellular bacterial pathogens, and antibacterial concentrations at this site have been linked to treatment efficacy. The relevance of this tissue compartment for fungal lung infections is not clear.
Table 1 Comparative Pharmacokinetics of Antifungal Agents

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>AmB</th>
<th>ABCD</th>
<th>ABLC</th>
<th>LAB</th>
<th>Flu</th>
<th>Itr</th>
<th>Vor</th>
<th>Pos</th>
<th>Anid</th>
<th>Casp</th>
<th>Mica</th>
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</thead>
<tbody>
<tr>
<td>Oral bioavailability, %</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>95</td>
<td>50</td>
<td>96</td>
<td>8–47</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
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<tr>
<td>Food effect</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No Effect</td>
<td>Increased absorption</td>
<td>No effect</td>
<td>Increased absorption</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Acid effect</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No effect</td>
<td>Pill—increase absorption</td>
<td>Oral solution—decrease absorption</td>
<td>No effect</td>
<td>Increased absorption</td>
<td>NA</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>10</td>
<td>99.8</td>
<td>58</td>
<td>99</td>
<td>84</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Minor hepatic</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Minor</td>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life, h</td>
<td>50</td>
<td>30</td>
<td>173</td>
<td>100–153</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Usual dose*</td>
<td>0.3–1.0 mg/ kg/d</td>
<td>3–6 mg/ kg/d</td>
<td>5 mg/ kg/d</td>
<td>3–5 mg/ kg/d</td>
<td>400–800 mg/d</td>
<td>600 mg/d for first three days, then 200 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic drug monitoring target</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&gt;1–2 μg/mL</td>
<td>&gt;1–2 μg/mL</td>
<td>&gt;0.5–1.5 μg/mL</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dosing in renal insufficiency</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Decrease Dose</td>
<td>Caution with IV preparation for CrCl &lt; 30 mL/ min</td>
<td>Caution with IV preparation for CrCl &lt; 50 mL/ min</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Dosing in hepatic insufficiency</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Decrease dose for mild to moderate cirrhosis</td>
<td>No change</td>
<td>No change</td>
<td>Decrease dose for moderate insufficiency</td>
<td>No change</td>
</tr>
</tbody>
</table>

AmB, amphotericin B; ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; LAB, liposomal amphotericin B; Flu, fluconazole; Itr, itraconazole; Vor, voriconazole; Pos, posaconazole; Anid, anidulafungin; Casp, caspofungin; Mic, micafungin; NA, not applicable. Data are derived from References 3–50.

*Usual dose administered in a therapeutic setting.

Target concentrations represent serum trough concentrations associated with treatment efficacy (i.e., not prophylaxis targets).
this apparent PK advantage with drug efficacy relative to the other AmB formulations. In one analysis, rabbits were administered AmB deoxycholate (AMB), AmB colloidal dispersion (ABCD), AmB lipid complex (ABLC), or liposomal AmB (LAMB) for 8 days. After the last dose the animals’ drug concentrations in ELF, pulmonary alveolar macrophages (PAMs), and lung tissue were measured. The concentration of drug in lung tissue and PAMs was impressive in the ABLC-treated animals, with a 70- to 375-fold increased concentration of drug noted in lung tissue or PAMs compared with serum levels. In a murine invasive pulmonary aspergillosis (IPA) model, the dose–response relationships and lung concentrations of ABLC and LAMB were compared. At 5 mg/kg/d, there was faster clearance of fungal burden in the lungs in the ABLC group. The significance of these PK differences in patients with pulmonary fungal infection remains unknown.

Several PK differences have been delineated for drugs from the triazole class. Fluconazole is available in oral and intravenous formulations. Oral absorption is predictable and near 90%. The drug penetrates all tissues, including near 90% accumulation in ocular and CNS sites. The drug is minimally metabolized and cleared almost entirely by the kidneys. Dose reduction is recommended with marked renal dysfunction. Voriconazole is available in oral and a cycloextrin intravenous formulation. The oral formulation is well absorbed and optimal without food. The drug accumulates in most infection sites, including the CNS and eye. Voriconazole undergoes extensive metabolism to inactive compounds. Common genetic polymorphisms in the primary metabolic enzyme (CYP2C19) result in variable serum concentrations. A number of studies have demonstrated the importance of monitoring trough serum concentrations to guide therapy. Renal dysfunction does not impact voriconazole but does impact cycloextrin in the intravenous formulation. Current recommendations suggest use of the parenteral formulation only in patients with creatinine clearance > 50 mL/min. However, accumulating case series describe use in patients with renal insufficiency that has not been associated with toxicity.

Itraconazole is available as an oral capsule, oral cycloextrin solution, and intravenous cycloextrin solution. The oral absorption is erratic, leading to unpredictable drug concentrations at the site of infection. The solution is better absorbed (about 30% more) than the capsule. Absorption of the capsule is optimal with higher gastric acidity and food. The solution is not impacted by acid and is best absorbed without a meal. Numerous clinical studies have demonstrated the utility of trough serum concentration monitoring to guide dosing. The drug distributes well to most infection sites with the exception of the CNS and eye. Renal and hepatic dysfunction does not mark-

edly impact kinetics. However, similar to the intravenous formulation of voriconazole, the cycloextrin-containing parenteral drug is not recommended in patients with significant renal insufficiency. Posaconazole is available as an oral formulation. The pharmacokinetic properties of posaconazole are similar to the itraconazole capsule with respect to variability, impact of gastric acid, and food. Recent clinical series have suggested the importance of serum concentration monitoring.

A common pharmacokinetic characteristic of all triazoles is the potential for drug interactions, mostly due to inhibition or induction of a variety of CYP450 enzymes. The impact of each drug on these enzymes varies among compounds. Extensive review of this important topic is beyond the scope of the current article but has been recently well detailed by Nivoix et al.

Each of the three clinically available echinocandins is available for intravenous use. Distribution is extensive with the exception of the CNS and ocular tissues. Drug interactions are uncommon and of minimal clinical relevance. Renal dysfunction does not impact kinetics of these compounds. However, dose reduction is recommended for caspofungin with marked hepatic insufficiency.

PHARMACODYNAMIC PRINCIPLES

The study of antimicrobial pharmacodynamics (PD) provides insight into the link among drug PK, in vitro susceptibility, and treatment efficacy. Understanding of PK/PD principles can provide useful information for the clinician to choose the most potent drug and provides a guide to the most efficacious and safe dose and interval of administration for a particular pathogen and infection site. Three traditional PD indices have been used to describe these relationships (Fig. 1). Each of these drug exposure indices represents a measure of drug PK relative to the MIC of the infecting organism. The PD indices include the peak concentration in relation to the MIC (Cmax/MIC), the area under the concentration curve in relation to the MIC (24 h area under the concentration curve [AUC]/MIC), and the time that drug concentrations exceed the MIC expressed as a percentage of the dosing interval (%T > MIC). Knowledge of which of the three PD indices describes antifungal activity provides the basis for determining the frequency with which a drug is most efficaciously administered. For example, if the Cmax/MIC index relationship strongly correlates with activity of drug A, the optimal dosing schedule would provide large, infrequent doses. Conversely, if the %T > MIC better describes drug activity, a dosing strategy may include smaller, more frequent drug administration to prolong the period of time that drug levels exceed the MIC.

PD studies can also define the amount of antimicrobial relative to the MIC that is needed for efficacy.
This drug exposure indexed to the MIC is termed the PD target. For example, if %T > MIC is the PD index linked to efficacy, the PD target is how much time concentrations need to exceed the MIC for optimal efficacy.

Three types of experimental studies have been used to delineate PD characteristics. The first study design involves investigation of the antifungal drug antimicrobial activity over time. Two outcomes are commonly noted. First is the impact of increasing drug concentrations on the rate and extent of organism killing. When higher concentrations enhance killing, the drug is referred to as concentration dependent. The second study end point includes examination of antifungal activity after drug concentrations decrease to below the organism MIC. For some drugs there is a period of prolonged growth suppression following an initial supra-MIC exposure.\(^{51}\) This period of growth suppression is termed a postantifungal effect (PAFE). Three combinations of these time-kill end point characteristics have been observed, and each combination is predictive of one of the PD indices. The Cmax/MIC is associated with concentration-dependent killing and prolonged PAFEs. The %T > MIC is associated with concentration-independent killing and short PAFEs. The AUC/MIC is associated with prolonged PAFEs and either concentration-dependent or -independent killing.

The second study type used to determine which PD index is predictive of efficacy is termed dose fractionation. Traditional dose escalation studies use a single dosing interval. With only a single dosing interval, escalating doses increase the values of all three indices. Dose fractionation studies examine efficacy of various dose levels that are administered by using three or more dosing intervals. In examining treatment results, if the regimens with shorter dosing intervals are more efficacious, the time-dependent index (T > MIC) is the more important parameter. If the large, infrequently administered dosing regimens are more active, the Cmax level in relation to the MIC is most predictive. Finally, if the outcome is similar with each of the dosing intervals, the outcome depends on the total dose or the AUC for the dosing regimen.

The third approach is used to determine the amount of drug or index magnitude that is required for treatment efficacy. These studies can be used to help answer numerous questions related to the exposure response relationship. For example, what PD magnitude of a drug is needed to treat an *Aspergillus* infection? Is this PD magnitude the same as that needed to treat infection due to other fungal pathogens? for different infection sites? in different animal species? The answers to these questions have been explored and most successfully addressed using various in vivo infection models. The results of these studies have demonstrated that the magnitude of a PD index associated with efficacy is similar for drugs within the same class, provided that free drug levels are considered. Furthermore, these data show that the index magnitude associated with efficacy is independent of the animal species, dosing interval, site of infection, and most often, the infecting pathogen. Most important, correlation of human PK and clinical trial outcome with several antifungal agents has suggested the magnitude of the PD index that produces efficacy in animal models also predicts efficacy in humans.\(^{1,4,52}\)

The PD evaluation of each antifungal drug class and the clinical implications of these studies are detailed here.

**Antifungal Pharmacodynamics**

Extensive experimental and clinical antifungal PD studies have been undertaken relative to invasive candidiasis (Table 2). Fewer investigations have addressed these questions for fungi that produce primary fungal pneumonia. However, thus far the observations from study of fungi such as *Aspergillus* species have been quite similar to those with *Candida* species.

**AMPHOTERICIN B**

In vitro and in vivo PD studies with AmB against *Candida* species have observed enhanced killing as the concentration of AmB is escalated multiple times higher than the MIC.\(^{7,51,53-59}\) These studies have further shown that fungal growth is inhibited for long periods following AmB exposure, or prolonged postantifungal suppression.

![Figure 1](image_url)  
**Figure 1** Pharmacokinetic–pharmacodynamic relationship of antifungal drug concentration over time relative to organism minimum inhibitory concentration (MIC, dashed line). Pharmacodynamic indices include the maximum or peak drug concentration relative to MIC (Cmax/MIC), the area under the drug concentration curve (shaded area) relative to MIC (AUC/MIC), and time that the concentration of drug exceeds the MIC (time > MIC). Also shown is the postexposure period, which represents the period of time of drug exposure that is below the MIC in which a number of antifungals express continued antifungal effect, termed the postantifungal effect (PAFE).
Prolonged PAFEs should allow for wider spacing of the dosing intervals. The PD characteristics of concentration-dependent killing and prolonged PAFEs would support once-daily administration of maximally tolerated doses. The $C_{\text{max}}$/MIC index has been most closely linked to treatment efficacy, and results of PD target investigations have consistently shown increased killing as the concentration of drug exceeds the MIC from two- to 10-fold.

An in vitro PD study by Lewis et al examined the impact of AmB concentration against *Aspergillus* and other filamentous fungi. The findings demonstrated concentration-dependent reduction in organism burden of nearly 4 log$_{10}$ over a 100-fold range in drug levels. These results were quite similar to those described in *Candida* models. In a similar fashion, an in vivo PD study by Wiederhold et al examined AmB PD characteristics using a murine model of IPA with *A. fumigatus*. Three dose levels and three dosing intervals were delivered to infected neutropenic and corticosteroid-suppressed mice. At the end of the 4-day study period treatment efficacy was assessed by qPCR and animal survival. For each of the three dose levels, the most widely spaced dosing interval (ie, large doses given infrequently) produced the greatest reduction in lung *Aspergillus* burden, and PD modeling suggested that the $C_{\text{max}}$/MIC index was most closely linked to treatment effect.

Despite the large amount of clinical trial data on AmB, very few of these studies provide data that would allow PD analyses. We are aware of a single study in pediatric patients where individual patient PK data, MIC of the infecting organism, and clinical outcome were collected. In this small cohort, a subset had *Aspergillus* infections, maximal efficacy was observed when the $C_{\text{max}}$/MIC of LAMB was greater than 40. Given the potency differences between DAMB and LAMB (roughly fivefold), the results are remarkably congruent with preclinical models.

**TRIAZOLEs**

The triazole antifungal class is perhaps the most well studied antifungal group in terms of PD analyses. Observations from these investigations demonstrated time-dependent antifungal activity that was optimal at concentrations one to two times the MIC. In addition, in vivo studies have revealed prolonged periods of growth suppression following triazole exposure. These characteristics are consistent with drugs for which the AUC/MIC index is most closely linked with efficacy. PD target data with each of the triazoles against multiple *Candida* isolates have observed efficacy associated with free drug (non–protein bound) 24-hour AUC/MIC values near 25. This is essentially similar to averaging a serum concentration near the MIC for a day or one times the MIC times 24 hours. Clinical trial data from mucosal and systemic candidiasis have identified a similar PD target for fluconazole and voriconazole. The PD study of the triazoles against pulmonary fungal pathogens is limited. We are not aware of published investigations exploring the impact of concentration and dose fractionation. However, two groups have designed experiments to define the PD target for voriconazole and posaconazole in invasive aspergillosis models. Mavridou et al utilized a nonneutropenic

<p>| Table 2 Pharmacodynamic Characteristics and Therapeutic Drug Targets in Systemic Antifungal Therapy against <em>Candida</em> and <em>Aspergillus</em> Species |</p>
<table>
<thead>
<tr>
<th>Antifungal Class</th>
<th>PD Characteristics</th>
<th>PD Target* Candida spp.</th>
<th>PD Target* Aspergillus spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration</td>
<td>Time</td>
<td>Index</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Dependence</td>
<td>Dependence</td>
<td>Predictive of Efficacy</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td>Cmax/MIC</td>
<td>2–4</td>
</tr>
<tr>
<td>Amphotericin B lipid formulations</td>
<td>X</td>
<td>X</td>
<td>Cmax/MIC</td>
</tr>
<tr>
<td>Triazoles</td>
<td>X</td>
<td>X</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>X</td>
<td>X</td>
<td>AUC/MIC</td>
</tr>
</tbody>
</table>

PAFE, postantifungal effect; PD, pharmacodynamic.
*PD target magnitude calculated using free drug concentrations (i.e., % drug not protein bound).
Based on a single study.
1Based on patient therapeutic drug monitoring data.
murine model of disseminated aspergillosis to define the voriconazole 24 h AUC/MIC target for *Aspergillus fumigatus*. The group utilized four strains with voriconazole MICs that varied eightfold. Using animal survival as an end point, maximal efficacy was observed at 7 days with a free drug AUC/MIC value of 36 (fairly similar to that described for *Candida* species). The same group performed similar studies with posaconazole. The total drug AUC/MIC value associated with maximal survival over 14 days for the four *Aspergillus* strains was a value near 1000 (this would be a free drug value near 10). Howard et al utilized a murine, neutropenic and corticosteroid model of pulmonary aspergillosis to explore the relationship between posaconazole 24-hour AUC/MIC and efficacy. Animals were infected with a single strain of *Aspergillus fumigatus*, and serum galactomannan was utilized as the study end point after 96 hours of therapy. The end points were expressed as the proportion of maximal galactomannan reduction over the posaconazole dose range. Maximal (90%) reduction was observed at a 24-hour AUC/MIC value of 440 (using total drug concentrations, free drug would be a value near 4). The relatively small differences in PD target may be due to differences in end point or infection model (disseminated vs pulmonary infection).

Clinical data to allow PD target exploration for patients with IPA remain limited. The only data that allow some analyses are found in the study of the relationship between triazole therapeutic drug monitoring and efficacy.21,22,44,78 Combining the drug-monitoring data, human PK data for the drug, and treatment outcome, one can mathematically estimate the PD drug exposures that are associated with efficacy in patients with IPA. In more than 80 patients receiving voriconazole for invasive aspergillosis for whom there were drug monitoring and clinical outcome data, clinical success and survival were significantly higher in patients who achieved serum trough concentrations from 1 to 2 μg/mL.21,22 Taking the free drug AUCs associated with these concentration levels and the MIC90 for *Aspergillus* isolates in these two studies, the resulting 24-hour AUC/MIC value is approximately 25. A subset of patients from a salvage trial of posaconazole for invasive pulmonary aspergillosis allows similar analyses.44 Among the 67 patients with posaconazole serum concentration monitoring there was a clear dose–response relationship over four concentration quartiles. The group that experienced maximal response (75%) had an average serum posaconazole concentration of 1.25 μg/mL. Although MIC testing was not available to make AUC/MIC calculations in this group, these data nonetheless highlight the important PD relationships that can be gleaned from clinical data and the utility of therapeutic drug monitoring, which has become standard of practice for these two drugs.

**Echinocandins**

Extensive PD study has been completed with each of the available echinocandins for *Candida* species. Experimental models have found concentration-dependent activity with a prolonged PAFE similar to that observed with AmB.58,79–90 The concentration-dependent indices, Cmax/MIC and AUC/MIC, have both been closely linked to efficacy and supporting a dosing strategy in which large doses are administered infrequently. PD target investigations in both animal models and patients with invasive candidiasis have identified similar values with maximal efficacy reported at free-drug AUC/MIC values near 10.

Limited PD exploration has been undertaken with this drug class for pulmonary fungal pathogens. The echinocandins affect the growth of *Aspergillus* species differently than *Candida*. Against *Aspergillus* species they exhibit a fungistatic effect. Distinct morphological changes occur with echinocandin exposure, and it is thought this is due to concentration of β-(1,3)-D-glucan within the apical tips of the growing hyphae.93 Phenotypically, what one observes is highly branched, swollen, short, stubby hyphal tips. These observable phenotypic changes in growth are utilized in the microbiology lab to determine the minimum effective concentration (MEC) of echinocandins, which is used in place of MIC. Therefore, using MEC as the measure of in vitro potency, PD index evaluation has also been performed in invasive aspergillosis models.92–95 Similar to the *Candida* models, Cmax/MEC was the PD index that was associated with treatment efficacy. PD target analysis in pulmonary aspergillosis models is sparse. A single study quantifying the Cmax/MEC ratio associated with maximal efficacy found a PD target ratio between 10 and 20.92 Although this is slightly higher than that noted in *Candida* models, this may not be surprising given the differing effects this class has on the two genera (cidal against *Candida* and static against *Aspergillus*).

Examination of these PD relationships in the clinical realm is limited to patients with invasive candidiasis only. There are numerous clinical trials (often retrospective and observational) that support echinocandin use in patients with pulmonary aspergillosis. However, PD analysis to justify and potentially optimize their use in these patients is lacking and urgently needed.

**Combination Therapy**

Despite advances in antifungal drug development, treatment outcomes remain dismal for many pulmonary fungal infections. One treatment strategy of growing interest for these difficult-to-treat infections is combining two or more antifungal drugs from distinct drug classes. The success of this approach for treatment of invasive fungal infections has been demonstrated for the combination of AmB and flucytosine in management of
cryptococcal meningitis. However, discerning the utility of drug combinations is complex. Many biological and study design factors can impact the outcome determination. Numerous in vitro and animal model studies have tested the efficacy of a variety of combinations for treatment against pulmonary fungal infections. The majority of investigations have targeted filamentous fungi such as *Aspergillus* species. The drug combinations most commonly considered include AmB with a triazole or an echinocandin with a triazole. Outcomes of these experiments have varied from demonstration of enhanced to reduced efficacy. For example, a polyene with triazole in animal models of aspergillosis was shown to be antagonistic by Lewis et al and Meletiadis et al, but potentially additive with improved survival in a CNS model developed by Clemons et al. A potential explanation for the lack of increased efficacy with these two agents is that they have similar targets within the fungus. Therefore, the more intensely studied combination has been an echinocandin and triazole. Although Luque et al found indifference with micafungin and itraconazole combination therapy in a murine systemic invasive aspergillosis model, many others have shown beneficial effects from improved survival to additive and synergistic microbiological effects. For example, both Petraitis et al and Kirkpatrick et al were able to show both improved survival and reduction in CFUs for combination therapy with an echinocandin and triazole.

One factor of apparent importance is the concentration of the drug components. For example, in vitro interaction analysis in combination therapy performed by Meletiadis et al and O'Shaughnessy et al showed low AmB and triazole concentrations in combination with intermediate echinocandin concentrations to be the most synergistic in triple combination therapy models. In vivo animal model analysis has revealed equally interesting concentration-dependent effects in combination therapy. In a neutropenic rabbit model, addition of low concentrations of anidulafungin to voriconazole was synergistic by Bliss independence analysis of residual fungal burden, pulmonary infarct scoring, and CT scan results. In contrast, high concentrations of anidulafungin with voriconazole were antagonistic by Bliss independence analysis of residual fungal burden, pulmonary infarct scoring, and CT scan results. In vivo animal model analysis has revealed equally interesting concentration-dependent effects in combination therapy. In a neutropenic rabbit model, addition of low concentrations of anidulafungin to voriconazole was synergistic by Bliss independence analysis of residual fungal burden, pulmonary infarct scoring, and CT scan results. In contrast, high concentrations of anidulafungin with voriconazole were antagonistic by Bliss independence analysis of residual fungal burden, pulmonary infarct scoring, and CT scan results. In contrast, high concentrations of anidulafungin with voriconazole were antagonistic by Bliss independence analysis of residual fungal burden, pulmonary infarct scoring, and CT scan results. In contrast, high concentrations of anidulafungin with voriconazole were antagonistic by Bliss independence analysis of residual fungal burden, pulmonary infarct scoring, and CT scan results.

Several clinical reports suggest the utility of combination therapy using a triazole and an echinocandin in patients with pulmonary aspergillosis. However, it is important to note that the majority of these reports are retrospective and salvage–treatment cohorts. There are at this time, no prospective, randomized trials of combination therapy; however, an ongoing trial comparing anidulafungin plus voriconazole to voriconazole alone (using standard doses of both) is scheduled to be finished in 2011. Although the infectious disease community eagerly awaits these results, one might still wonder, if these results are positive, negative, or indifferent at standard doses of the two drugs, could alternative doses or dosing strategies yield increased synergistic interactions and improve patient outcomes even more? Combination therapy PD analyses to tease out these complex relationships are urgently needed and will be vital in designing future clinical trials that have the highest predicted value of success. Most importantly, they will be fundamental elements in improving the dismal outcomes we continue to observe with these difficult infectious diseases.

CONCLUSIONS

Optimal use of antifungal drugs requires knowledge of key PK and PD characteristics. Application of PD principles to antifungal drug therapy of *Candida* and *Aspergillus* infections has provided an understanding of the relationship between drug dosing and treatment efficacy. Although there remain many unanswered questions, available data suggest usefulness in the application of PD to clinical practice. Future application of these principles should aid in the design of optimal combination antifungal therapies.

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