Integrating MIC and PK/PD properties of anti-fungal drugs

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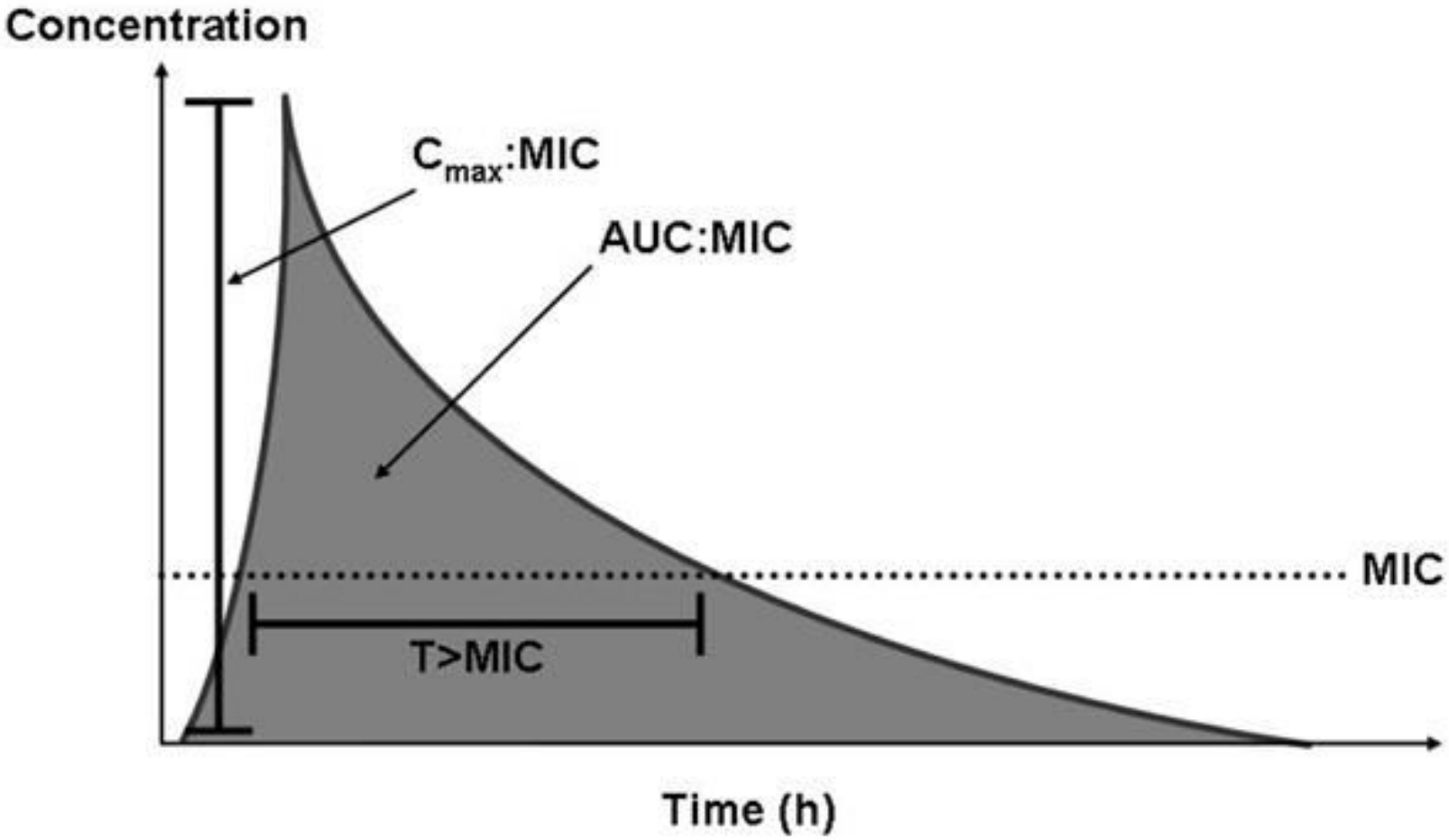
Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.

MIC is generally regarded as the most basic laboratory measurement of the activity of an antimicrobial agent against an organism

Different experimental conditions accounts for discordant MICs as determined by CLSI and EUCAST methodologies.

For the bridging process, an assumption is made that the same methodology is used to determine the MIC in the experimental system and patients.

Clinically, the minimum inhibitory concentrations are used not only to determine the **amount of antibiotic that the patient will receive but also the type of antibiotic used,** which in turn lowers the opportunity for microbial resistance to specific antimicrobial agents.

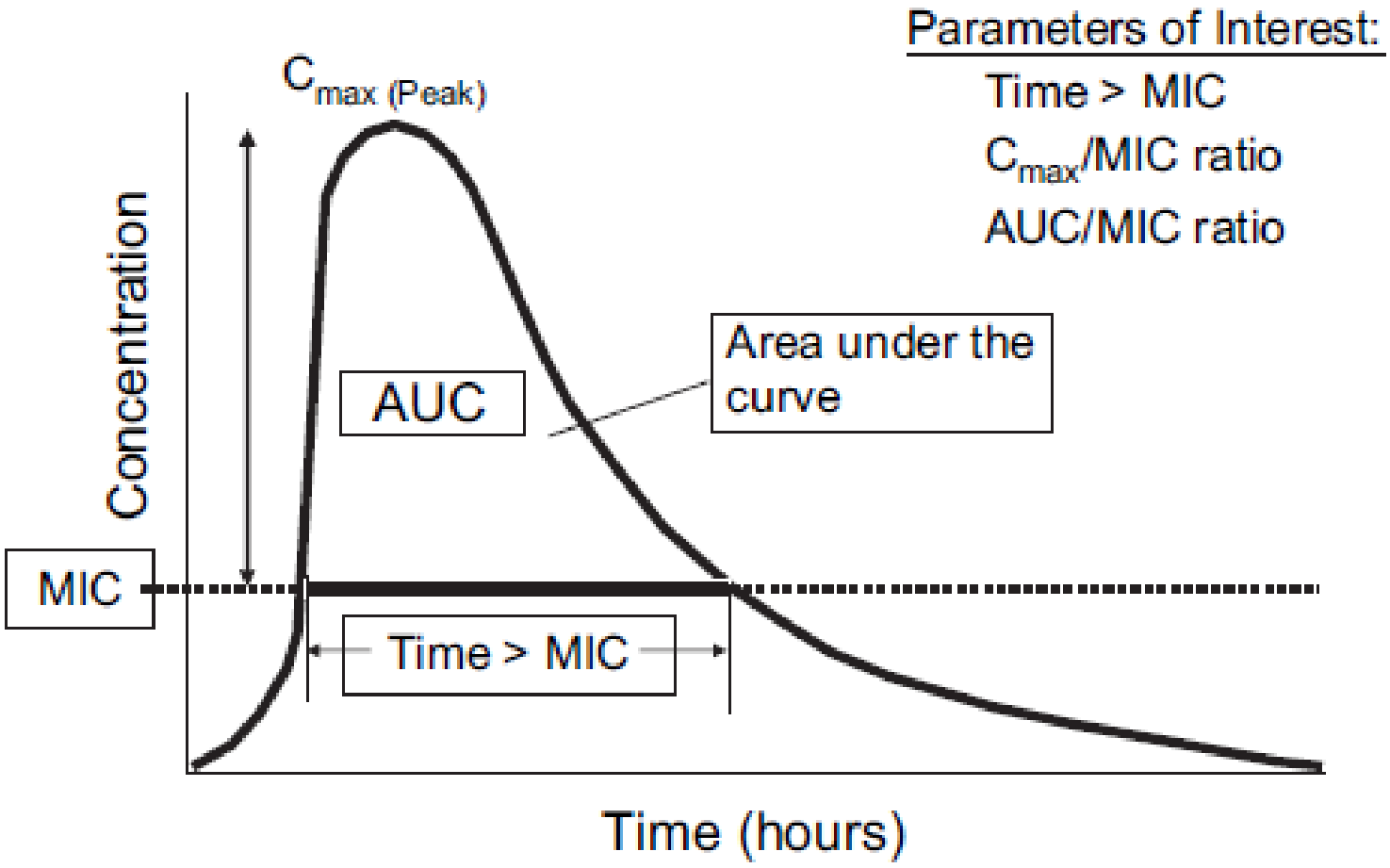

Concentration
C_{max}:MIC
AUC:MIC
MIC
T>MIC
Time (h)

Pharmacokinetic / pharmacodynamic (PK/PD) investigations have been valuable for

Defining optimal antifungal dosing regimens and developing **in vitro susceptibility breakpoints**

Clinical trial development, and for development of microbiology **laboratory guidelines**

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.


Parameters of Interest:
Time > MIC
C_{max}/MIC ratio
AUC/MIC ratio
$C_{max\ (Peak)}$
Concentration
AUC
Area under the curve
MIC
Time > MIC
Time (hours)

Three traditional pharmaco-dynamic parameters cand be derived :

Peak concentration in relation to the MIC (Cmax/ MIC),

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)

The Cmax/MIC is associated with concentration-dependent killing and prolonged PAFEs.

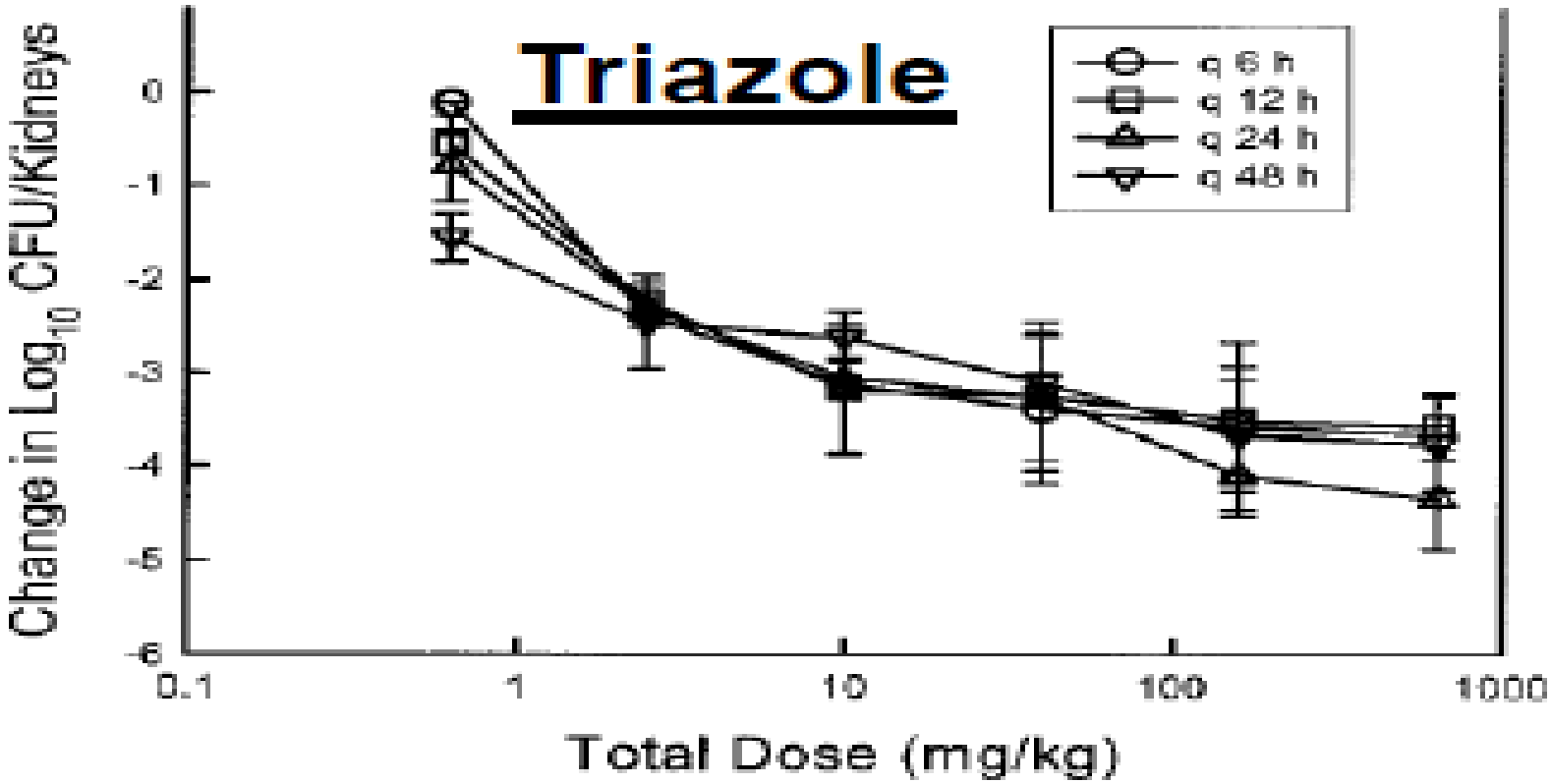
The %T > MIC is associated with concentration-independent killing and short PAFEs.

The AUC/MIC is associated with prolonged PAFEs and either concentration-dependent or -independent killing.

Triazole pharmacodynamics

Studies with fluconazole, posaconazole, ravuconazole, and voriconazole demonstrated that outcome was independent of fractionation of the total drug exposure supporting the 24-hour AUC/MIC as the pharmacodynamic parameter driving treatment efficacy

The triazole AUC/MIC associated with efficacy in these studies was similar for susceptible C albicans and those with reduced susceptibility caused by target site mutations and over expression of several drug efflux pumps



- Outcome independent of dosing interval

Clinical impact

The largest data to produce MIC is summarized in the Clinical Laboratory Standards Institute (CLSI) antifungal susceptibility breakpoint guideline publication. Data from six fluconazole trials include nearly 500 episodes of oropharyngeal candidiasis in which the organism MIC, drug dose, and clinical outcomes were available

When the 24-hour fluconazole AUC/MIC exceeded a value of 25, clinical treatment success was observed in 91% to 100% of patients.

When this pharmacodynamic value decreased to less than 25, however, treatment failures were reported in 27% to 35% of cases.

The association between the 24-hour AUC/MIC and outcome is similar to that observed in animal model pharmacodynamic studies.

In patients with deep Candida infection it is difficult to show a relationship between MIC and outcome, because the AUC/MIC values are above a value at which one expects failures related to drug therapy

Clinical success was observed in 70% of patients when the fluconazole AUC/MIC ratio was 25 or greater and was 47% when the value decreases to less than 25 .

Susceptibility breakpoints of 16 to 32 mg/L for doses of 400 to 800 mg/d for candidemia was observed

Polyene pharmacodynamics

In vitro and in vivo studies has demonstrated marked concentration dependent killing and maximal antifungal activity at concentrations exceeding the MIC from 2- to 10-fold.

Maximal killing was similarly observed with doses that produce serum concentrations exceeding the MIC from 4- to 10-fold. The AmB products also produced prolonged in vivo PAFEs.

Each of the lipid formulations is complexed to a different lipid and exhibits unique pharmacokinetic characteristics.

The liposomal formulation of AmB achieves high serum concentrations relative to those achieved by the other formulations. Maximal efficacy was observed with liposomal AmB serum Cmax/MIC ratios greater than 40

Conversely, following administration of the lipid complex formulation of AmB, serum levels are low, yet the distribution to certain organs, such as the lungs, is reported to exceed those of the other formulations.

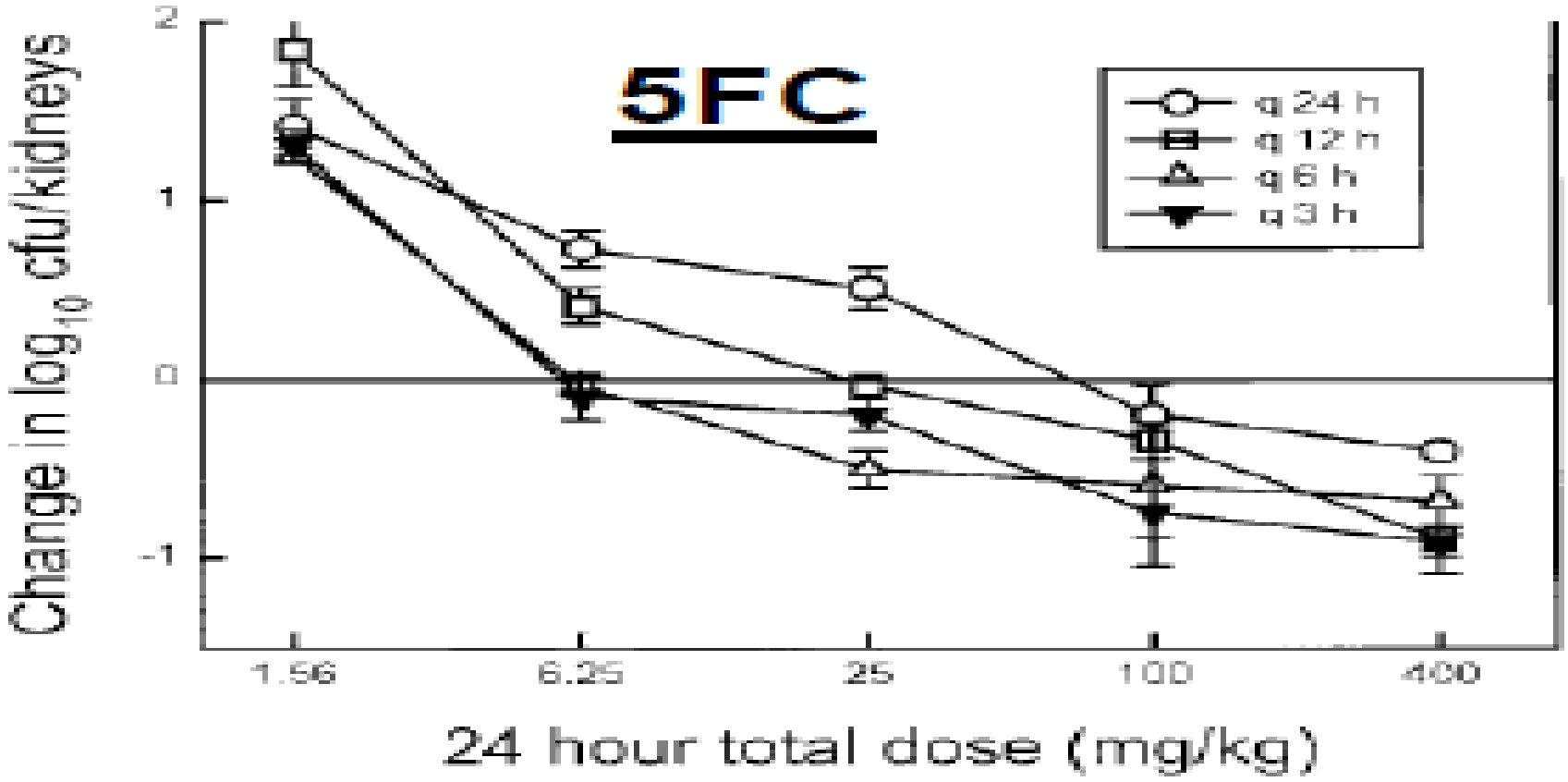
The lipid formulations were 4.3- to 5.9-fold less potent than conventional AmB

Flucytosine pharmacodynamics

Increasing drug concentrations in vitro and larger doses in vivo produced minimal concentration-dependent killing of Candida species and soon after exposure organism growth resumes

The time course and dose fractionation results in therapy against C albicans suggest the %T > MIC would be the most predictive parameter.

Studies of flucytosine in an in vivo Aspergillus model also suggests that the most fractionated regimen (every 6 as opposed to every 12 or 24 hours) was most effective.



- Outcome better with small frequent administration

bone marrow toxicity is observed when levels in serum exceed 50 to 60 mg/L

150 mg/kg/d divided into four doses, each dose of 37.5 mg/kg would remain higher than the MIC for 90% of C albicans isolates tested for 12 to 14 hours

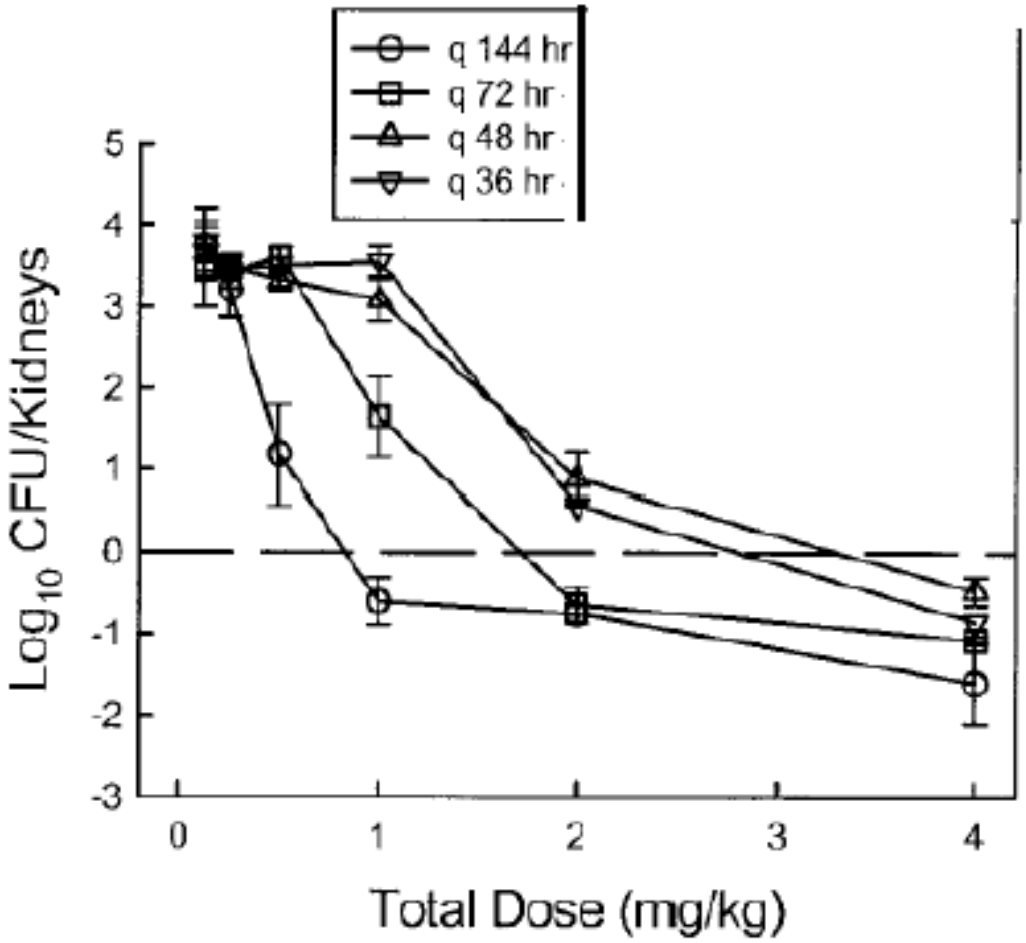
Echinocandin pharmacodynamics

In vitro time course studies with each of the available echinocandin drugs have demonstrated concentration-dependent killing and prolonged PAFEs similar to those observed with the polyenes.

In vivo studies have confirmed these pharmacodynamic characteristics

Andes D Antimicrob Agents Chemother 2003;47:1187–92.
Walsh TJ,. Antimicrob Agents Chemother 1991;35:1321–8.

Echinocandin Dosing Interval and C. albicans



- Outcome better with large doses given less frequently

The total amount of drug necessary to achieve various microbiologic outcomes over the treatment period was **4.8- to 7.6-fold smaller** when the dosing schedule called for large single doses than when the same amount of total drug was administered in two to six doses

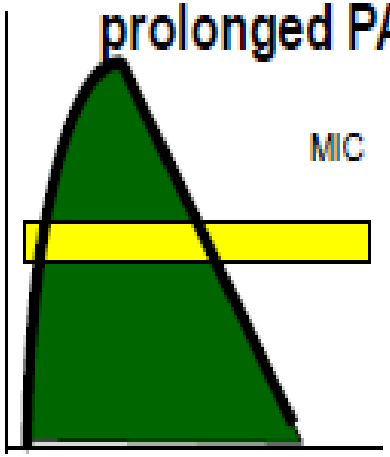
The concentration-dependent killing pattern and results from dose fractionation studies would suggest that either the Cmax/MIC or AUC/MIC would best represent the driving pharmacodynamic parameter

In vivo studies using serum kinetics suggest that the Cmax/MIC was better predictive of efficacy

Maximal efficacy when the total drug Cmax/MIC of approached a value of 10 (net inhibitory outcomes were observed with values near 3).

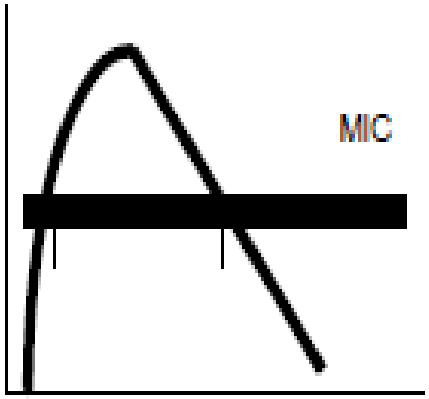
In a pulmonary aspergillosis model, caspofungin efficacy was similarly maximized at a Cmax/MIC ratio in the range of 10 to 20

Peak/MIC or AUC/MIC
(concentration-dependent prolonged PAFE)



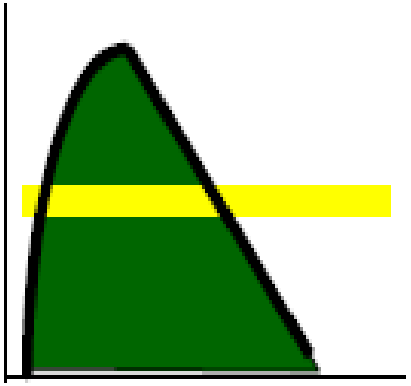
Amphotericin
Echinocandins

Time >MIC
(time-dependent killing short or not PAFE)



Flucytosine

AUC_{24} /MIC
(time-dependent killing prolonged PAFE)



Triazoles

DISTINCT PK/PD PROFILES

Limitations of pharmacodynamic models

Some pharmacodynamic studies use only a single well-characterized laboratory strain, which may leave questions as to the applicability of conclusions for a wider population of organisms

Laboratory animal models generally mimic acute rather that chronic invasive syndromes; these syndromes are difficult to simulate in a reproducible manner

a delay in the administration of antifungal therapy results in diminished antifungal effect

organisms with a faster rate of growth are killed more rapidly

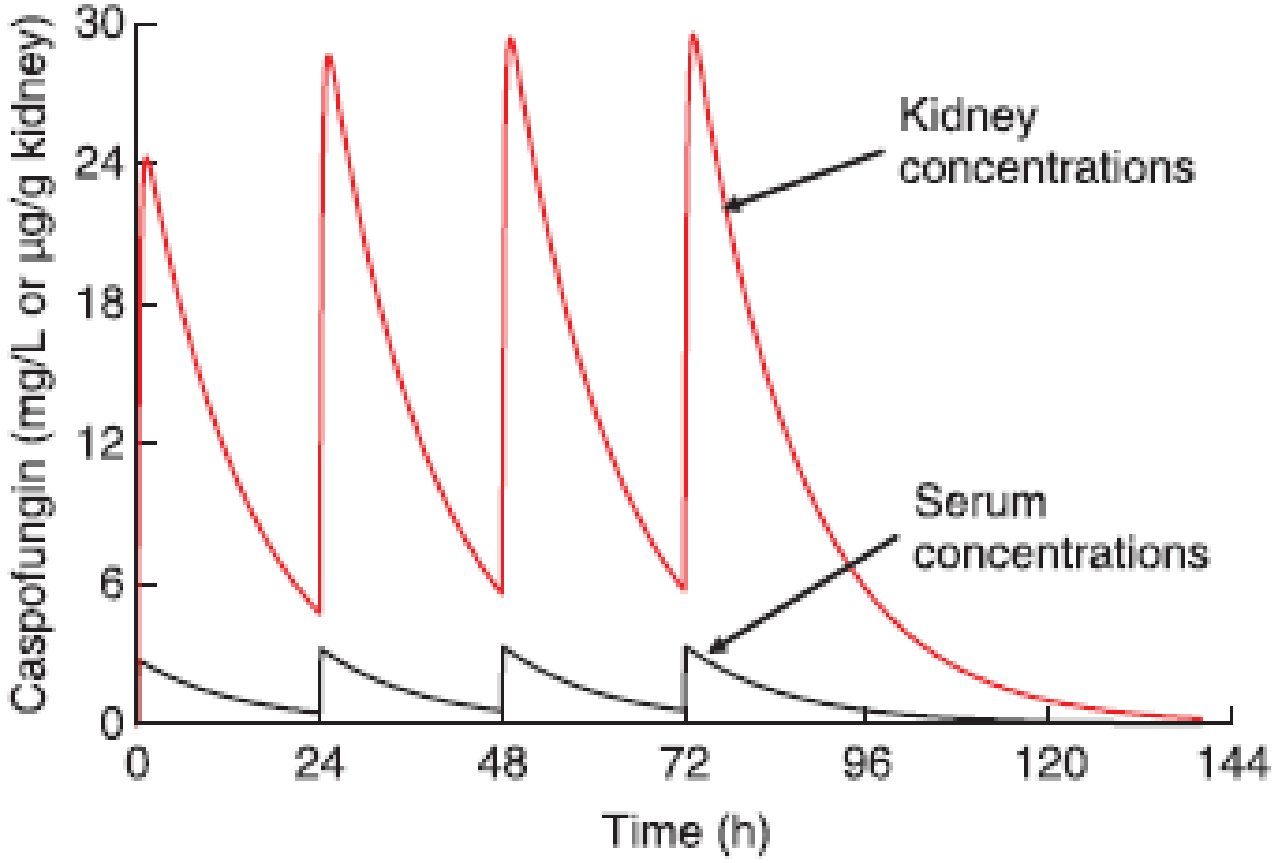
The antifungal effect is greater in the presence of immunological effectors

Frequently, plasma concentrations are a perfectly acceptable surrogate for concentrations at the site of infection, even in circumstances where the concentrations in tissues significantly deviate from those measured in plasma.

If concentrations of antifungal agents in plasma and tissues scale proportionally, but there is significantly delayed trafficking of drug into or out of tissues, then the antifungal effect may become dissociated from plasma concentrations; this phenomenon is called hysteresis.

The echinocandins and the triazoles are two classes of antifungal agents that exhibit prolonged mean residence times within tissues, and the antifungal effect may be best understood by considering tissue concentrations over time

The relationship between plasma and tissue concentrations of various clinical formulations of amphotericin B is less well defined and studies are going on !



This figure depicts the concentration–time profile of caspofungin in the serum and kidneys of mice. Concentrations are much higher in the kidney and persist long after serum concentrations decline to undetectable levels. For caspofungin, the antifungal effect is best understood by considering tissue concentrations, although it is still possible to link serum concentrations with the observed effect

Concentrations of drug can also be measured in bodily fluids such as epithelial lining fluid of the lung (ELF), cerebrospinal fluid (CSF), urine, and sinus aspirates.

A decision must be made whether these compartments are relevant to the pathogenesis of the infectious process

Protein binding

Flucytosine, for example, is negligibly bound . The triazoles display variable degrees of protein binding ranging from low (e.g. fluconazole 10%), intermediate (e.g. voriconazole c. 60%) to high (e.g. isavuconazole and posaconazole, >90%). The echinocandins are extensively protein bound (>90%). The binding properties of amphotericin B are very poorly understood.

There is little understanding of the effect of the drug binding within tissues and the resultant impact on the antifungal effect

For a neutropenic host, a target associated with near maximal killing may be desirable.

In contrast, for non-neutropenic hosts, lesser degrees of antifungal killing may suffice, because of the additional antifungal effect of immunological effectors

Pediatric patients often exhibit more rapid linear clearance of voriconazole, which may result in low or undetectable serum drug concentrations at standard adult doses.

Therefore, higher weight-based doses are recommended in children (7 mg/kg every 12 hours, sometimes increased up to 12 mg/kg every 12 hours without a loading dose)

Polymorphisms in the CYP2C19-encoding gene result in 3 populations of patients with markedly different rates of nonlinear voriconazole clearance despite the administration of the same fixed daily dose:
(1) homozygous patients who extensively metabolize voriconazole,

(2) heterozygous patients with moderate clearance rates of voriconazole, and

(3) Homozygous patients who metabolize drug poorly through this pathway and have slow rates of voriconazole clearance.

There is no way of knowing whether a pharmacodynamic target is necessarily meaningful for clinical contexts—this must be determined by extensive cross validation with clinical data,

Without direct measurement of drug concentrations, the extent of inherent pharmacokinetic variability is undefined, and the impact of this variability on clinical outcome is not apparent

SUMMARY

Application of pharmacodynamic principles to antifungal drug therapy of Candida and Aspergillus infections has provided an understanding of the relationship between drug dosing and treatment efficacy

Observations of the pharmacodynamics of triazoles and AmB have correlated with the results of clinical trials and have proven useful for validation of in vitro susceptibility breakpoints.

Future application of these principles should aid in the design of optimal combination antifungal therapies

Thanks