Dosing should be such that the level of antmicrobial activity is associated with a high likelihood of therapeutic success.

![Dose-Response Graph]

**Disclosures**

Research grants – advisory boards – speaker

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**PK/Pd of antifungal drugs**

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**Dosing** should be such that the level of antmicrobial activity is associated with a high likelihood of therapeutic success.
Efficacy of the drug

Potency of a drug \( (\text{MIC}) \)

Exposure to the bug \( \text{in vivo} \) \( (\text{PK}) \)

Potency of a drug \( \text{in vitro} \) \( (\text{MIC}) \)

Exposure to the bug \( \text{in vivo} \) \( (\text{PK}) \)

Antimicrobial Efficacy of the Drug
(\text{Microbiological Cure})

Effect on Host
(\text{Clinical Cure})

ACTIVITY
\( \text{in vitro} \) \( (\text{MIC}) \)

CONCENTRATIONS
\( \text{in vivo} \) \( (\text{PK}) \)

DOISING regimen

ANTMICROBIAL EFFICACY
(\text{Microbiological Cure})

Other factors

CLINICAL EFFICACY
(\text{Clinical Cure})
Treatment with fluconazole
Doses 50 – 800 mg

Culture-results with
MIC-values

Individual Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)

Clinical outcome

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Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

• Prob cure correlates with Dose/MIC
• POSITIVE correlation with Dose
• INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain Dose/MIC value

Rodriguez-Tudela et al, AAC 2007

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Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

Pharmacodynamic Target

NOTE: MICs by EUCAST method

Rodriguez-Tudela et al, AAC 2007
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

Pharmacodynamic Target
Uncertainty

NOTE: MICs by EUCAST method
Rodriguez-Tudela et al, AAC 2007

Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

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Rodriguez-Tudela et al, AAC 2007

Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

IF MIC = 4 mg/L
WHAT IS THE LOWEST DOSE YOU ARE COMFORTABLE WITH?

Dose
1. 200 mg
2. 400 mg
3. 800 mg
4. 1600 mg

Pharmacodynamic Target
Rodriguez-Tudela et al, AAC 2007
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

IF Dose = 400 mg
WHICH MIC ARE YOU COMFORTABLE WITH?

1. 1 mg/L
2. 2 mg/L
3. 4 mg/L
4. 8 mg/L

Pharmacodynamic Target

- If The standard dose is 400 mg
- It follows that the breakpoint is 400/100 = 4 mg/L

Note: This breakpoint may be altered with legitimate changes in circumstances.

Susceptible (S)
A micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.

Intermediate (I)
A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system. Note: This breakpoint may be altered with legitimate changes in circumstances.

Resistant (R)
Bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system. Note: This breakpoint may be altered with legitimate changes in circumstances.

WWW.EUCAST.ORG
Problem (or is it?):

What if the standard dose is different?
What if the population is different?

ACTIVITY
in vitro (MIC)

CONCENTRATIONS
in vivo (PK)

DOISING regimen

ANTMICROBIAL EFFICACY
(Microbiological Cure)

Other factors

CLINICAL EFFICACY
(Clinical Cure)
ACTIVITY in vitro (MIC) → CONCENTRATIONS in vivo (PK) → DOSING regimen

ANTIMICROBIAL EFFICACY (Microbiological Cure)

Other factors

CLINICAL EFFICACY (Clinical Cure)

Pharmacokinetic parameters: Measures of Exposure

AUC is usually linearly related to Dose
AUC is usually linearly related to Dose

Dose x 2 = AUC x 2
Dose x 4 = AUC x 4

So what determines the relationship between dose and exposure?

Fluconazole Dose - AUC Relationship

Rodriguez-Tudela et al, AAC 2007
So what more determines the relationship between dose and exposure?

Pharmacokinetics

- Some patients are more equal than others
auc distribution fluconazole
monte carlo simulation

Exposure by MIC of fluconazole

Monte Carlo Simulations

volunteer data 400 mg/dose

MIC mg/L

AUC/MIC

MIC mg/L

AUC/MIC

Eucast rationale document, 2007
Exposure by MIC of fluconazole Monte Carlo Simulations

volunteer data 400 mg/dose

MIC mg/L

AUC/MIC

1000
100
10

Average

1
2
4
8
16
32

10
100
1000

Average

95% CI

99% CI

Exposure by MIC of fluconazole Monte Carlo Simulations

volunteer data 400 mg/dose

MIC mg/L

Target AUC/MIC ratio = 50
Target Dose/MIC ratio = 100

Eucast rationale document, 2007
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**LAB REPORT**

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)

**BASED ON EXPOSURES OF COMMON DOSES**
Exposures in children: differences

- Lower EXPOSURE than expected
- Clearance in individual

Pharmacokinetic parameters of Fluconazole by age group

AUC per unit dose (mg/kg) of fluconazole differences by age group

AUC per unit dose (mg/kg) of fluconazole

MCS of fluconazole: variability in children

400 mg dose in adults compares to ~ 20 mg/kg
Exposures in children:

- Generally lower – increase dose
- Larger variability – be aware, possible increase dose or monitor or estimate clearance
- These insights can help to rationalize dosing regimens in children

To summarize:

- There is a good relationship for exposure and response
- This translates to dosing regimens for the general population
- Breakpoints are based on the most common lowest dose
- Other populations may require dose adjustments
- For non-predictable concentrations: TDM is a requirement