Dosing should be such that the level of antifungal activity is associated with a high likelihood of therapeutic success.
Treatment with fluconazole
Doses 50 – 800 mg

Culture-results with MIC-values

Determine Dose/MIC for each patient

Individual Dose

MIC-values per individual

Microbiological outcome (candida cured)

Clinical outcome

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

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

- **Prob cure correlates with Dose/MIC**
- **POSITIVE correlation with Dose**
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Each data point represents the proportion of patients cured within a group representing a certain Dose/MIC value

Rodriguez- Tudela et al, AAC 2007

**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

Rodriguez- Tudela et al, AAC 2007
**EUCAST**

**EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING**

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.

**Susceptible (S)**

- **Susceptible (S)**
- **Intermediate (I)**
- **Resistant (R)**

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

**Pharmacodynamic Target**

- 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

**Probability of cure after treatment with fluconazole**

**Oropharyngeal Candidiasis n=132**

- **EC50**
- **R²**

**Dose/MIC**

**IF Dose = 400 mg**

- **Rodriguez- Tudela et al, AAC 2007**

If the standard dose is 400 mg, it follows that the breakpoint is 400/100 = 4 mg/L.
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) → DOSSING regimen

ANTIMICROBIAL EFFICACY (Microbiological Cure)

Other factors → CLINICAL EFFICACY (Clinical Cure)

AUC is usually linearly related to Dose

Pharmacokinetic parameters: Measures of Exposure

Mouton et al., Drug Resistance Updates 2011
AUC is usually linearly related to Dose.

\[ \text{Dose} \times 2 = \text{AUC} \times 2 \]
\[ \text{Dose} \times 4 = \text{AUC} \times 4 \]

So what determines the relationship between dose and exposure?
So what more determines the relationship between dose and exposure?
auc distribution fluconazole
monte carlo simulation

Exposure by MIC of fluconazole
volunteer data 400 mg/dose

Monte Carlo Simulations
Eucast rationale document, 2007

© by author
Exposure by MIC of fluconazole
Monte Carlo Simulations

volunteer data 400 mg/dose

Average

MIC mg/L

AUC/MIC

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

95% CI

99% CI
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.

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.

A micro-organism is 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.

LAB REPORT

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

BASED ON EXPOSURES OF COMMON DOSES

IN ADULTS
Exposures in children: differences

- Lower EXPOSURE then expected
- Clearance in individual

Pharmacokinetic parameters of Fluconazole by age group

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


ESCMID Online Lecture Library © by author
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