EUCAST breakpoints

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Professor pharmacokinetics and pharmacodynamics
LAB REPORT

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

### Sensitivity

<table>
<thead>
<tr>
<th>Organism 1</th>
<th>Escherichia coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoeveelheid</td>
<td>$\geq 10^5$ kve/ml</td>
</tr>
<tr>
<td>Panel gevoeligheid</td>
<td>5 Urine Coliform</td>
</tr>
<tr>
<td>amoxicillin/clavula</td>
<td>Sensitive (0.06 mg/l)</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>Sensitive (0.06 mg/l)</td>
</tr>
<tr>
<td>cefuroxim</td>
<td>Sensitive (0.06 mg/l)</td>
</tr>
<tr>
<td>cefotaxim</td>
<td>Sensitive (0.5 mg/l)</td>
</tr>
<tr>
<td>cefazoline</td>
<td>Sensitive (1.25 mg/l)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>Sensitive (0.06 mg/l)</td>
</tr>
<tr>
<td>doxycycline</td>
<td>Sensitive (1 mg/l)</td>
</tr>
<tr>
<td>nitrofurantoin</td>
<td>Sensitive (0.06 mg/l)</td>
</tr>
<tr>
<td>norfloxacin</td>
<td>Intermediate (1 mg/l)</td>
</tr>
<tr>
<td>sulfamethoxazole</td>
<td>Sensitive (0.5 mg/l)</td>
</tr>
<tr>
<td>tobramycin</td>
<td>Intermediate (0.25 mg/l)</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>Resistant (&gt;64 mg/l)</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>Sensitive (1 mg/l)</td>
</tr>
<tr>
<td>ceftazidim</td>
<td>Sensitive (0.13 mg/l)</td>
</tr>
</tbody>
</table>
Is susceptibility (MICs) related to (clinical) outcome?

If yes, which values (breakpoints) make the difference?
Potency of a drug \textit{in vitro} (MIC)

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

Dosing Regimen

Antimicrobial Efficacy of the Drug (Microbiological Cure)

Effect on Host (Clinical Cure)

Mouton et al., \textit{Drug Resistance Updates 2011}
MIC
Measure of Potency

Lowest concentration with no visible growth after 18 hour incubation

$\text{MIC} = 2 \text{ mg/L}$
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

Rodriguez- Tudela et al, AAC 2007
Probability of cure after treatment with fluconazole

Oropharyngeal Candidiasis  n=132

• If Dose/MIC of 100 is required

• It follows that the breakpoint is 400/100 = 4 mg/L

Probability of cure after treatment with fluconazole

Rodriguez- Tudela et al, AAC 2007
Antimicrobial Treatment
Pharmacokinetic parameters: Measures of Exposure

AUC is usually linearly related to dose.
Pharmacokinetic parameters:
Measures of Exposure

AUC is usually linearly related to Dose

Dose x 2 = AUC x 2
Dose x 4 = AUC x 4
Lowest concentration with no visible growth after 18 hour incubation

**MIC**

<table>
<thead>
<tr>
<th>.25</th>
<th>.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
</table>

**PK**

X-acin 500 mg

**MIC = 2 mg/L**
Pharmacokinetic Parameter (and Dose)

- Thus, we have to:
  - Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
  - Determine which dosing regimens are optimal for Treatment in relation to the MIC
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 breakpoints 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.
We aim for:

- Hitting the PK/PD target
- A high likelihood of success for every one (s)
SETTING A BREAKPOINT – PK/PD (example 1)

DETERMINE THE PK/PD TARGET e.g. value of the PK/PD Index (animal studies, clinical studies)

ESTIMATE EXPOSURE from the dosing regimen and PK, including population variability

CALCULATE PK/PD BREAKPOINT from $PK/PD$ target = $PK/PD$ Index
SETTING A BREAKPOINT – PK/PD (example 1)

1. DETERMINE THE PK/PD TARGET: e.g. value of the PK/PD Index (animal studies, clinical studies)

2. ESTIMATE EXPOSURE: from the dosing regimen and PK, including population variability

3. CALCULATE PK/PD BREAKPOINT: from \( PK/PD \) target = \( PK/PD \) Index
Any idea where we are today?

No idea…

may be a mouse?

Might be a human, though…
An elephant....
Today it is an elephant!
THE TARGET IS THE MICRO-ORGANISM
Neutropenic Mouse Thigh-Infection Model

1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1
2. Bacteria injected into thighs on day 0 ($10^{4-7}$)
3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days
4. Mortality
A clear relationship exists between exposure and effect

A maximum effect is reached at ratio's of 25-35 (mortality)

Relationship between \( fAUC/MIC \) and Effect

121 patients with \( S. pneumoniae \) respiratory infection

- \( fAUC/MIC \) cut-off \( \sim 34 \)

- Relationship between \( fAUC:MIC \) ratio & microbiological response from a total 121 patients with respiratory tract infection involving \( S. pneumoniae \).
- \( fAUC:MIC > 34 \) had 92.6% response rate.
- \( fAUC:MIC < 34 \) had 66.7% response rate.
Quantitative relationship: exposure in mice and men

AUC/MIC
mouse

AUC/MIC
human

Mortality (%)
0
20
40
60
80
100

24-Hr AUC/MIC

~ 30-35

Probability of eradication

fAUC_{24}:MIC Ratio

r^2 = 0.90

Ciprofloxacin
Garenoxacin
Gatifloxacin
Grepafloxacin
Levofloxacin
Neutropenic Mouse Thigh-Infection Model

1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1

2. Bacteria injected into thighs on day 0 ($10^{4-7}$)

3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days

4. Thighs removed, homogenized, serially diluted and plated for CFU determinations
Curve / effect description

Inoculum

In Vivo Static Effect

50% Emax

90% Emax

100% Emax

no effect

log cfu

log (auc) levofloxacin

© by author
Curve / effect description

- Inoculum

- In Vivo Static Effect
  - 50% Emax

- One log drop Effect
  - 90% Emax
  - 100% Emax

- No effect
24-Hr AUC/MIC with Total and Free Drug for the Static Dose of Different Fluoroquinolones with *S. pneumoniae* ATCC 10813
Pharmacodynamic target exposure in mice and men

AUC/MIC human

~ 30-35

AUC/MIC mouse

24-Hr AUC/MIC

Probability of Eradication

\( r^2 = 0.90 \)

\( fAUC_{24}:MIC \) Ratio

Mortality (%)
SETTING A BREAKPOINT – PK/PD (example 1)

DETERMINE THE PK/PD TARGET  
  e.g. value of the PK/PD Index  
  (animal studies, clinical studies)

ESTIMATE EXPOSURE  
  from the dosing regimen and PK, including population variability

CALCULATE PK/PD BREAKPOINT  
  from $PK/PD \text{ target} = PK/PD \text{ Index}$
GOOD Clinical Practice

Be sure that the fAUC/MIC ratio is at least appr. 34 in every patient

AUC

MIC
Levofloxacin 500 mg

\[ fAUC = 30-50 \text{ mg/L} \]
Clinical practice:

When starting treatment, we do not know:

- the AUC in the individual patient
Pharmacokinetics

Some people are more equal than others...
fAUC distribution levofloxacin
(monte carlo simulation)
fAUC distribution levofloxacin
(monte carlo simulation)
On the average, this duck is dead
SETTING A BREAKPOINT – PK/PD (example 1)

- **DETERMINE THE PK/PD TARGET**
  - e.g. value of the PK/PD Index
  - (animal studies, clinical studies)

- **ESTIMATE EXPOSURE**
  - from the dosing regimen and PK, including population variability

- **CALCULATE PK/PD BREAKPOINT**
  - from $PK/PD \ target = PK/PD \ Index$
The fAUC is calculated for 10,000 patients using MCS. This results in a probability distribution of AUCs. The fAUC/MIC is calculated for each MIC.

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levofloxacin 500 mg x 1 oral

Mouton et al., 2004
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levofloxacin 500 mg x 1 oral

95% percentile
99% percentile
mean

Mouton et al., 2004
The fAUC is calculated for 10,000 patients using MCS. This results in a probability distribution of AUCs. The fAUC/MIC is calculated for each MIC.

Mouton et al., 2004
levofloxacin 500 mg x 1 oral

$S = 1 \text{ mg/L}$

EUCAST., 2004

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ESCMID Online Lecture Library
Levofloxacin / Streptococcus pneumoniae
Antimicrobial wild type distributions of microorganisms – reference database

EUCAS

MIC
Epidemiological cut-off: WT ≤ 2 mg/L

18248 observations (9 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L
High dose levofloxacin
2x 500 mg, or 750 mg
AUC 70-80

Target
35 = 70 / 2
**Ciprofloxacin 500 mg q12h oral**

- **MIC mg/L**

- **fAUC/MIC**

- **99% CI**

- **Average**

- **He chose poorly**

- *-Knight from Indiana Jones: The Last Crusade*
Be sure that the \( f\text{AUC}/\text{MIC} \) ratio is at least appr. 34 in every patient.

This includes patients with a high clearance.

Bugs with MICs that can be expected.
SETTING A BREAKPOINT – PK/PD (example 2)

DETERMINE THE PK/PD TARGET  e.g. value of the PK/PD Index

ESTIMATE EXPOSURE  from the dosing regimen and PK, including population variability

CALCULATE PK/PD BREAKPOINT  from $\text{PK/PD target} = \text{PK/PD Index}$
Are All Antimicrobials Created Equal???
Pharmacokinetic parameters:
Measures of Exposure
Time > MIC dependent on dose frequency

Total daily dose similar

Total length of bars corresponds to Time > MIC
Literature Review for T>MIC for Beta-Lactams Versus Mortality in Animal Models

- At least 48 hours of treatment
- Mortality 80-100% in untreated controls
- Pharmacokinetics provided to calculate magnitude of PK/PD parameter
- Mortality recorded within 24 hrs after last dose of drug
- Data from 3 animal species and 4 sites of infection

Craig CID 26:1, 1998; Nicolau et al. AAC 44:1291, 2000
Ceftazidime PD in neutropenic mice

Static %fT>MIC 39.1 %
<table>
<thead>
<tr>
<th>Drug</th>
<th>Enterobacteriaceae</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (T)</td>
<td>72 (66-79)</td>
<td>74 (69-78)</td>
</tr>
<tr>
<td>Ceftriaxone (F)</td>
<td>38 (34-42)</td>
<td>39 (37-41)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>38 (36-40)</td>
<td>38 (36-40)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>36 (27-42)</td>
<td>39 (35-42)</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>35 (29-40)</td>
<td>37 (33-39)</td>
</tr>
</tbody>
</table>

Data from Craig
Protein binding:
Effect on Penetration of β-Lactams into Rabbit Peripheral Lymph

Correlation between protein binding and penetration

% Penetration of total drug (AUC lymph/AUC plasma)

Correlation between protein binding and penetration

Plasma binding %

G Woodnutt et al. AAC 1995, 39 (12)
Activity of 4 Cephalosporins against Various Enterobacteriaceae with and without ESBLs

Craig & Andes ICAAC 2005
Clinical phase 3 study

PK-data

PK population model

Individual PK parameters

Culture-results with MIC-values

MIC-values per individual

Individual exposure to CAZ

%fT>MIC

Microbiological outcome

Clinical outcome
Ceftazidime in patients with nosocomial pneumonia

- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - Extensive and sparse sampling of ceftazidime

- Numbers of patients in CAZ arm:
  
  \[ \text{N}=390 \text{ patients included} \]
  \[ \Downarrow \]
  
  \[ \text{N}=170 \text{ with MIC} \]
  \[ \Downarrow \]
  
  \[ \text{N}=154 \text{ with MIC and PK-estimates} \]
  
  220 without Gram negatives in cultures
  
  16 without PK estimates

Muller et al, JAC 2013 68:900-906
PK/PD of ceftazidime in Clinical Study

- 154 patients with nosocomial pneumonia (including VAP)
- PK parameters determined in every patient
  - Sparse sampling; covariates; population PK
- MICs of infecting micro-organisms
- Individual exposures to CAZ (%fT>MIC) Categorised (%fT>MIC per 10%)
- Eradication rate per exposure group

Muller et al, JAC 2013 68:900-906
Exposure-response Emax model

ceftazidime – micro eradication

- Baseline response 50%
- Max response 99.7%
- 50% Effective PD index ($E_{I50}$): 47 %$fT>MIC$

Muller et al, JAC 2013 68:900-906
Ceftazidime in patients with nosocomial pneumonia

CART analysis
to differentiate between lower and higher response rate

%T>MIC breakpoint = 44.9%
P< 0.0001

<table>
<thead>
<tr>
<th>%T&gt;MIC</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥44.9</td>
<td>83 (90.2%)</td>
<td>9 (9.8%)</td>
</tr>
<tr>
<td>&lt;44.9</td>
<td>31 (50%)</td>
<td>31 (50%)</td>
</tr>
</tbody>
</table>
Probability plot of the logistic regression analysis for ceftazidime showing the relationship between $\%fT>MIC$ (Gram-negatives at baseline/EOT) and probability of cure at TOC.

Muller et al, JAC 2013 68:900-906
Ceftobiprole \( \%fT>\text{MIC} \) (\textbf{Gram-negatives} at baseline/EOT) and probability of cure at TOC (nosocomial pneumonia [excl. VAP, n=82])
Quantitative relationship: exposure in mice and men

\[ fT>MIC \]

mouse

\[ fT>MIC \]

human

~40-50%

<table>
<thead>
<tr>
<th>%fT&gt;MIC</th>
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</tbody>
</table>

%fT>MIC breakpoint = 44.9 %

P < 0.0001
Probability of Target Attainment - Ceftazidime

EUCAST rationale document

BP = 4 mg/L
<table>
<thead>
<tr>
<th>Disease state, drug</th>
<th>Clinically-derived PK-PD target [reference(s)]</th>
<th>Animal infection model; organism studied</th>
<th>Animal-derived PK-PD target [reference(s)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-acquired pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>$fAUC_{0-24}:MIC$ ratio, 62–75 [11, 12]</td>
<td>Neutropenic mouse thigh; gram-negative bacilli</td>
<td>$fAUC_{0-24}:MIC$ ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]</td>
</tr>
<tr>
<td>Community-acquired respiratory tract infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>$fAUC_{0-24}:MIC$ ratio, 34 [22]</td>
<td>Immune competent mouse thigh; <em>Streptococcus pneumoniae</em></td>
<td>$fAUC_{0-24}:MIC$ ratio, 25–34 for 90% animal survival or 2 log-unit kill [23]</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>$T&gt;MIC$, 40% of the dosing interval [14]</td>
<td>Immune competent mouse thigh; <em>S. pneumoniae</em></td>
<td>$T&gt;MIC$, 30–40% of the dosing interval for 90% animal survival [14]</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>$AUC_{0-24}:MIC$ ratio, 3.375 [20]</td>
<td>Neutropenic mouse thigh; <em>S. pneumoniae</em></td>
<td>$AUC_{0-24}:MIC$ ratio, 1000 for stasis [24]</td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oritavancin</td>
<td>$fT&gt;MIC$, 22% of the dosing interval for <em>Staphylococcus aureus</em> [25]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$fT&gt;MIC$, 20% of the dosing interval for a 0.5 log-unit kill [26]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$AUC_{0-24}:MIC$ ratio, 85 for <em>S. aureus</em> or <em>Enterococcus faecium</em> [27]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$AUC_{0-24}:MIC$ ratio, 83 for stasis [33]</td>
</tr>
<tr>
<td>Complicated skin and skin structure infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>$AUC_{0-24}:MIC$ ratio, 17.9 [28]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$AUC_{0-24}:MIC$ ratio, 15–20 for stasis [29]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$AUC_{0-24}:MIC$ ratio, 110 [27]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$AUC_{0-24}:MIC$ ratio, 83 for stasis [33]</td>
</tr>
</tbody>
</table>

**NOTE.** $AUC_{0-24}:MIC$, the ratio of the area under the concentration-time curve at 24 h to the MIC; $C_{max}:MIC$, the ratio of the maximal drug concentration to the MIC; $T>MIC$, duration of time a drug concentration remains above the MIC.
Susceptible (S)

A micro-organism is defined as susceptible by a level of antmicrobial 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 antmicrobial 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 breakpoints may be altered with legitimate changes in circumstances.

Resistant (R)

Bacteria are defined as resistant by a level of antmicrobial 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.
The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

Preclinical PK/PD studies
- Correlation exposure–effect
  - Qualitative relationship (PK/PD index)
    - PD target
      - Clinical dosing regimen
        - Monte Carlo simulations
          - Initial PK/PD breakpoint
            - MCS robustness target population dose adjustments
              - PK/PD breakpoint
                - MIC distributions

Clinical PK/PD studies
- Correlation exposure - effect
  - Qualitative relationship (value PK/PD index)
    - PD target

FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.
Ciprofloxacin Rationale for the EUCAST clinical breakpoints, version 1.9
22 August 2007

Introduction

The fluoroquinolones comprise a class of agents derived from nalidixic acid and developed since the 1960s. The early fluoroquinolones had a limited spectrum of antibacterial activity, mainly against Gram-negative pathogens. The newer fluoroquinolone agents have enhanced intrinsic activity against Gram-positive organisms and anaerobes and improved pharmacokinetic characteristics in comparison with preceding derivatives. Emergence of resistance is mainly due to mutations in the QRDR region where phenotypic resistance arises as a result of stepwise mutations. Microorganisms may be mutation may exhibit elevated fluoroquinolone MICs that are sometimes difficult to distinguish from wild-type MIC distributions. Other low level resistance mechanisms include increased activity of efflux pumps, Qnr proteins (capable of protecting DNA gyrase from quinolones) and inactivating enzymes.

EUCAST has defined clinical breakpoints for the fluoroquinolones ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), norfloxacin (NOR) and ofloxacin (OFL). They are with few exceptions available in all European countries. Other fluoroquinolones which are available only in few countries or in topical preparations have not been addressed.

Some fluoroquinolones are available for both oral and intravenous therapy, while others are available for oral therapy only. This is reflected in the breakpoints.

Ciprofloxacin is used to treat complicated and uncomplicated urinary tract infections, acute and chronic bacterial prostatitis, gonorrhea, lower respiratory tract infections, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections and bloodstream infections, mainly involving Gram-negative organisms including Pseudomonas aeruginosa. It is also used in infectious diarrhoea caused by susceptible bacteria when antibacterial therapy is indicated. Other than in cystic fibrosis patients, where in cystic fibrosis patients is still a matter of debate.

1. Dosage

<table>
<thead>
<tr>
<th></th>
<th>BSAC</th>
<th>CA-SFM</th>
<th>CRG</th>
<th>DIN</th>
<th>NWpA</th>
<th>SRGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common dose (mg)</td>
<td>500 x 2 oral</td>
<td>500 x 2 oral</td>
<td>250 x 2 oral</td>
<td>500 x 2 oral</td>
<td>250-500 x 2 oral</td>
<td>500 x 2 oral</td>
</tr>
<tr>
<td>Maximum dose schedule (mg)</td>
<td>400 x 2 IV</td>
<td>200 x 2 IV</td>
<td>200 x 2 IV</td>
<td>200 x 2 IV</td>
<td>400 x 2 IV</td>
<td>400 x 2 IV</td>
</tr>
<tr>
<td>Available formulations</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
</tbody>
</table>

www.eucast.org
EUCAST Website resources

<table>
<thead>
<tr>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://www.EUCAST.org">http://www.EUCAST.org</a></td>
</tr>
<tr>
<td>All EUCAST documents FREE DOWNLOAD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EUCAST</th>
</tr>
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<tbody>
<tr>
<td><a href="http://mic.eucast.org/Eucast2">http://mic.eucast.org/Eucast2</a></td>
</tr>
<tr>
<td>MIC and zone diameter distributions</td>
</tr>
</tbody>
</table>

MIC distributions

Zone diameter distributions

MIC-zone diameter correlations
Implications for breakpoints

therapeutic success

PK/PD Index
Susceptibility (MICs) are related to (clinical) outcome.
Susceptibility (MICs) are related to (clinical) outcome?

Breakpoint values make the difference—but include PK!!!
Target Attainment

Mouton et al, Clin Ther 2005 27:762
Conclusions

• PK/PD breakpoints reflect the relationship between exposure and clinical outcome

• PK/PD breakpoints are dependent on dose (!), pharmacokinetic profile and pharmacodynamic target

• The pharmacodynamic target MAY differ by species (e.g. Gram- vs Gram+)

• EUCAST PK/PD breakpoints are based on clinical data if available and otherwise on animal data and other data. Rationale documents describe the background.