EUCAST breakpoints

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Disclosures

Research grants – advisory boards – speaker

LAB REPORT

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)
Is susceptibility (MICs) related to (clinical) outcome? If yes, which values (breakpoints) make the difference?

Efficacy of the drug

Potency of a drug (MIC) Exposition to the bug (PK)

ACTIVITY in vitro (MIC) CONCENTRATIONS in vivo (PK) DOSING regimen

ANTIMICROBIAL EFFICACY (Microbiological Cure)

Other factors

CLINICAL EFFICACY (Clinical Cure)
**MIC**

Measure of Potency

**MIC**

Lowest concentration with no visible growth after 18 hour incubation

**Dose/MIC**

- **EC50**: 43.69
- **R²**: 0.9938

**Probability of cure after treatment with fluconazole**

Oropharyngeal Candidiasis  n=132

- **Culture-results with MIC-values**
  - Individual Dose
  - MIC-values per individual
  - Determine Dose/MIC for each patient
  - Microbiological outcome (candida cured)
  - Clinical outcome

- **Probability of cure correlates with Dose/MIC**
- **POSITIVE** correlation with Dose
- **INVERSE** correlation with MIC

Rodriguez- Tudela et al, AAC 2007
If Dose is known because of the standard dose e.g. 400 mg ~ 400 mg/L
And a Dose/MIC of 100 is required
It follows that the breakpoint is 400/100 = 4 mg/L

It is thus, however, slightly more complicated than just dose........

- Usually, dose–effect relationships are not really known
- Development
- How to adjust for altered clearances

Dose is just a means to reach adequate concentrations

ACTIVITY
in vitro (MIC)

CONCENTRATIONS
in vivo (PK)

DOISING regimen

ANTIMICROBIAL EFFICACY
(Microbiological Cure)

OTHER factors

CLINICAL EFFICACY
(Clinical Cure)
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 = 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.

Intermediate (I)
A micro-organism is defined as intermediate by a level of antimicrobial activity associated with an indeterminate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

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.
A high likelihood of success for everyone (S)

WE AIM FOR:

Hitting the PK/PD target

### 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 $PK/PD \text{ target} = PK/PD \text{ Index}$ (animal studies, clinical studies)
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
4. Mortality

Neutropenic Mouse Model

1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1
2. Bacteria injected into thighs on day 0 (10^6 cfu)
3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days

5.106 cfu

Cyclophosphamide i.p.
Antimicrobial therapy s.c.

Time h

Treatment

-96 -24 -2.0 6 12 18 24

Homogenization thigh
CFU counts

Relationships Between 24-Hr fAUC/MIC and Efficacy against Pneumococci for Fluoroquinolones in Animals

- 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 ~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

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 (10⁶-7)
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

One log drop Effect

Plasma & Interstitial fluid

BOUND

FREE

BOUND

FREE
**Pharmacodynamic target**

exposure in mice and men

![Graph showing AUC/MIC exposure for mice and humans.]

**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
GOOD Clinical Practice

Be sure that the \(\text{fAUC/MIC} \) ratio is at least appr. 34 in every patient.

\[\text{AUC} \]
\[\text{MIC}\]

Clinical practice:

When starting treatment, we do not know:

- the AUC in the individual patient

Levofloxacin 500 mg

\(\text{fAUC} = 30-50 \text{ mg/L} \)
Pharmacokinetics

Some people are more equal than others…
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 (animal studies, clinical studies)

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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Mouton et al., 2004

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*levofloxacin 500 mg x 1 oral*

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*levofloxacin 500 mg x 1 oral*

Mouton et al., 2004
Levofloxacin / Streptococcus pneumoniae
Antimicrobial wild type distributions of pathogens – reference database

High dose levofloxacin
2x 500 mg, or 750 mg
AUC 70-80

Target
35 = 70 /2
"He chose poorly"
-Knight from Indiana Jones: The Last Crusade

GOOD Clinical Practice

Be sure that the fAUC/MIC ratios 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 PK/PD target = PK/PD Index
Are All Antimicrobials Created Equal???

Pharmacokinetic parameters: Measures of Exposure

Time > MIC dependent on dose frequency

Total daily dose similar
Infection Thigh model 2 strains/mouse, 1/ thigh

Cyclophosphamide i.p.
Antimicrobial therapy s.c.

Time h
-96 -24 -20 3 6 9 12 18 21 24
5.10^6 cfu

Homogenization thigh CFU counts

Efficacy Q3 > Q6 > Q12 > Q24 Primarily T (dependent)
Efficacy Q3 < Q6 < Q12 < Q24 Primarily Cmax (D) dependent
Efficacy Q3 = Q6 = Q12 = Q24 Primarily AUC (TDD) dependent

Levofloxacin in *S. pneumoniae* infection in mice

Relationship between T>MIC, Peak, AUC

Each dot represents one mouse / dosingregimen.

Based on data from Scaglione & Mouton, 2001, 2003
ESCMID Online Lecture Library © by author
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

Ceftazidime PD in neutropenic mice

Time > MIC Required for a Static Effect After 24-hours of Therapy with Four Cephalosporins

<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

Activity of 4 Cephalosporins against Various Enterobacteriaceae with and without ESBLs

Change in Log10 CFU/Thigh over 24 Hours

ESBLs
Non-ESBLs

Time Above MIC (percent)

Clinical phase 3 study
PK-data
PK population model
Individual PK parameters
Individual exposure to CAZ %fT>MIC
Microbiological outcome
Clinical outcome

ESBLs Non-ESBLs

Craig & Andes ICAAC 2005

PK-data Culture-results with and without ESBLs
MIC-values per individual

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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:
- N=390 patients included
- N=170 with MIC
- N=154 with MIC and PK-estimates
- 220 without Gram negatives in cultures
- 16 without PK estimates

Ceftazidime in patients with nosocomial pneumonia
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 (%T>MIC)
  - Categorised (%T>MIC per 10%)
- Eradication rate per exposure group

Exposure-response Emax model
- Baseline response 50%
- Max response 99.7%
- 50% Effective PD index (E150): 47 %T>MIC
Ceftazidime in patients with nosocomial pneumonia

Muller et al, JAC 2013 68:900-906

Probability plot of the logistic regression analysis for ceftazidime showing the relationship between %T>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC

Ceftobiprole %T>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC (nosocomial pneumonia [excl. VAP, n=82])

Muller et al., AAC 2014

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Quantitative relationship: exposure in mice and men

<table>
<thead>
<tr>
<th>Time Above MIC (% of Interval)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&gt;MIC mouse</td>
<td>~40-50%</td>
</tr>
<tr>
<td>T&gt;MIC human</td>
<td></td>
</tr>
</tbody>
</table>

**Quantitative relationship:**
exposure in mice and men

- **Mouse**:
  - Time Above MIC (% of Interval)
  - Mortality (%)

- **Human**:
  - Time Above MIC (% of Interval)
  - Mortality (%)

**Exposure in mice and men**

- **Bacterial Eradication (percent)**
  - 0 - 100%

**Probability of Target Attainment - Cefazidime**

- **Ceftazidime 1000 mg x3**
  - 95% percentile
  - Mean

**It is not only for Mice!!**

- **Ambrose et al, CID 2007**

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**EUCAST rationale document**

- **BP = 4 mg/L**

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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

Mouton et al, CMI 2012

www.eucast.org
EUCAST Website resources

- http://www.EUCAST.org
- All EUCAST documents FREE DOWNLOAD
- http://mic.eucast.org/Eucast2
- MIC distributions
- Zone diameter distributions
- MIC-zone diameter correlations

Implications for breakpoints

Susceptibility (MICs) are related to (clinical) outcome

High

Low
Susceptibility (MICs) are related to (clinical) outcome?

Breakpoint values make the difference – but include PK!!

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.