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)

<table>
<thead>
<tr>
<th>Organism 1</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>&gt;=10E5 kve/ml</td>
</tr>
<tr>
<td>5 Urine Coliform</td>
<td>Sensitive (0.06 mg/l)</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 (0.25 mg/l)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>Sensitive (&lt;=0.06 mg/l)</td>
</tr>
<tr>
<td>doxycycline</td>
<td>Sensitive (&lt;=1 mg/l)</td>
</tr>
<tr>
<td>nitrofurantoin</td>
<td>Sensitive (&lt;=32 mg/l)</td>
</tr>
<tr>
<td>norfloxacin</td>
<td>Intermediate (1 mg/l)</td>
</tr>
<tr>
<td>sulfamethoxazole</td>
<td>Intermediate (1 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?
Antimicrobial Efficacy of the Drug
(Microbiological Cure)

Potency of a drug
*in vitro* (MIC)

Exposure to the bug
*in vivo* (PK)

Dosing Regimen

Effect on Host
(Clinical Cure)
**MIC**

**Measure of Potency**

Lowest concentration with no visible growth after 18 hour incubation

![Image showing MIC values and a result of MIC = 2 mg/L](image)

**MIC**

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

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 = 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:

A high likelihood of success for every one (S)

Hitting the PK/PD target
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)

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 $PK/PD \text{ target} = PK/PD \text{ Index}$
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
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 \( \sim 34 \)

- 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

r² = 0.90

24-Hr AUC/MIC

fAUC₂₄/MIC Ratio

Ciprofloxacin
Garemoxacin
Gatifloxacin
Grepafloxacin
Levofloxacin

© by author
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
inoculum

Curve / effect description

In Vivo Static Effect
50% Emax
90% Emax
100% Emax

no effect
Curve / effect description

- Inoculum

- Log (auc) levofloxacin vs log cfu

- In Vivo Static Effect
  - 50% Emax
  - 90% Emax
  - 100% Emax

- One log drop Effect

- 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

~ 30-35

Mortality (%)

AUC/MIC mouse

AUC/MIC human

24-Hr AUC/MIC

Log_{10} CFU/Thigh at 24 Hrs

Probability of Eradication

fAUC_{24}:MIC Ratio

© by author
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 \( PK/PD \text{ target} = PK/PD \text{ Index} \)
Be sure that the $f\text{AUC}/\text{MIC}$ ratio is at least appr. 34 in every patient.
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
(animals 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.

Mouton et al., 2004

levofloxacin 500 mg x 1 oral

$\text{MIC mg/L}$

$\text{fAUC/MIC}$

95% percentile

99% percentile

mean
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

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levofloxacin 500 mg x 1 oral

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

S = 1 mg/L

95% percentile
99% percentile
mean

fAUC/MIC

MIC mg/L
Levofloxacin / Streptococcus pneumoniae
Antimicrobial wild type distributions of microorganisms – reference database
EUCARD
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

MIC mg/L

99% CI

Average

He chose poorly

-Knight from Indiana Jones: The Last Crusade
Be sure that the $fAUC$/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

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

- **PEAK**
- **AUC**
- **T > MIC**
- **MIC**
Time > MIC dependent on dose frequency

Total daily dose similar

12.5 q6
25 q12
50 q24

MIC 2 mg/L

Concentration mg/L

Time (h)

0 6 12 18 24

0 20 40 60 80 100

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 %
# 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

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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)

Plasma binding %

25 50 75 100

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

Drug Activity vs. Bacterial Growth

- Time Above MIC (%)
- Change in Log$_{10}$ CFU/Thigh over 24 Hours

ESBLs
- Initial CFU: 3
- Final CFU: -3
- Time Above MIC: 0 to 100%

Non-ESBLs
- Initial CFU: 3
- Final CFU: -3
- Time Above MIC: 0 to 100%

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

%\text{fT} > \text{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:

  - 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

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 (%$t>T>MIC)
  Categorised (%$t>T>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 (EI$_{50}$): 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

\[ \% T > \text{MIC} \text{ breakpoint } = 44.9 \% \]

\[ P < 0.0001 \]

<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>

Muller et al, JAC 2013 68:900-906
Probability plot of the logistic regression analysis for ceftazidime showing the relationship between \%\textit{fT}>\textit{MIC} (Gram-negatives at baseline/EOT) and probability of cure at TOC.

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

\[ fT > \text{MIC} \]
- mouse
- human

\[ fT > \text{MIC} \] breakthrough = 44.9%

\[ \text{P} < 0.0001 \]

<table>
<thead>
<tr>
<th>%( fT &gt; \text{MIC} )</th>
<th>Success</th>
<th>Failure</th>
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<td>&lt;44.9</td>
<td>31 (50%)</td>
<td>31 (50%)</td>
</tr>
</tbody>
</table>
Probability of Target Attainment - Ceftazidime

ceftazidime 1000 mg x3

\[ \text{Mean} \]

\[ \text{95\% percentile} \]

\[ \text{99\% percentile} \]

\[ \text{BP = 4 mg/L} \]

EUCAST rationale document
<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>$f\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 62–75}$ [11, 12]</td>
<td>Neutropenic mouse thigh; gram-negative bacilli</td>
<td>$f\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 70–90 for 90% animal survival or 2 log-unit kill}$ [13, 14]</td>
</tr>
<tr>
<td>Community-acquired respiratory tract infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>$f\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 34}$ [22]</td>
<td>Immune-competent mouse thigh; <em>Streptococcus pneumonia</em></td>
<td>$f\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 25–34 for 90% animal survival or 2 log-unit kill}$ [23]</td>
</tr>
<tr>
<td>$\beta$-Lactams</td>
<td>$T&gt;\text{MIC}, 40% \text{ of the dosing interval}$ [14]</td>
<td>Immune-competent mouse thigh; <em>S. pneumoniae</em></td>
<td>$T&gt;\text{MIC}, 30–40% \text{ of the dosing interval for 90% animal survival}$ [14]</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 3.375}$ [20]</td>
<td>Neutropenic mouse thigh; <em>S. pneumoniae</em></td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 1000 for stasis}$ [24]</td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oritavancin</td>
<td>$fT&gt;\text{MIC}, 22% \text{ of the dosing interval for Staphylococcus aureus}$ [25]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$fT&gt;\text{MIC}, 20% \text{ of the dosing interval for a 0.5 log-unit kill}$ [26]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 85 for S. aureus or Enterococcus faecium}$ [27]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 83 for stasis}$ [33]</td>
</tr>
<tr>
<td>Complicated skin and skin structure infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 17.9}$ [28]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 15–20 for stasis}$ [29]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 110}$ [27]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>$\text{AUC}_{0-24}: \text{MIC} \text{ ratio, 83 for stasis}$ [33]</td>
</tr>
</tbody>
</table>

**NOTE.** $\text{AUC}_{0-24}: \text{MIC}$, the ratio of the area under the concentration-time curve at 24 h to the MIC; $C_{\text{max}}: \text{MIC}$, the ratio of the maximal drug concentration to the MIC; $T>\text{MIC}$, duration of time a drug concentration remains above 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 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.
The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

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

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

**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
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**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 bactericidal 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 with such mutations 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. Older 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 its use in penetrating patients is still a matter of debate.

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### 1. Dosage

<table>
<thead>
<tr>
<th>BSAC</th>
<th>CA-SFM</th>
<th>CRG</th>
<th>DIN</th>
<th>NWGA</th>
<th>SRGA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common dose (mg)</strong></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>
</tr>
<tr>
<td>400 x 2 IV</td>
<td>200 x 2 IV</td>
<td>200 x 2 IV</td>
<td>100 x 2 IV</td>
<td>400 x 2 IV</td>
<td>400 x 2 IV</td>
</tr>
<tr>
<td><strong>Maximum dose schedule (mg)</strong></td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
</tr>
<tr>
<td>400 x 3 IV</td>
<td>400 x 3 IV</td>
<td>400 x 3 IV</td>
<td>400 x 3 IV</td>
<td>400 x 3 IV</td>
<td>400 x 3 IV</td>
</tr>
</tbody>
</table>

**Available formulations**

- oral, IV

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[www.eucast.org](http://www.eucast.org)
## EUCAST Website resources

<table>
<thead>
<tr>
<th>EUCAST</th>
</tr>
</thead>
</table>
| http://www.EUCAST.org  
All EUCAST documents FREE DOWNLOAD |

| http://mic.eucast.org/Eucast2  
MIC and zone diameter distributions |
| 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.