Towards Rational International Antibiotic Breakpoints:
Actions from the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

and some personal thinking…

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Based (largely) on presentations available from the EUCAST Web site, given to me by Gunnar Kahlmeter, or borrowed from Johan Mouton

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Why do we need breakpoints?

To be honest, I always wondered …
Why do we need breakpoints?

but perhaps…

1. Doctors like to know if the bug is "good" or "bad" …

2. Regulators like to tell people "DO" or "Don't"

3. Industry likes to know "When can I" and "When I cannot"

4. Lawyers like you to be "guilty" or "innocent" …

5. Microbiologists wish to give them all simple answers…
Simple answers …

- Good !!
- Bad !!
- May be?
Starting from the beginning… The MIC!

- Known quantity of bacteria placed into each tube
- Increasing antibiotic concentration
Starting from the beginning… The MIC!

24 h later ….

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

Increasing antibiotic concentration

0 µg/mL  0.25 µg/mL  0.5 µg/mL  1.0 µg/mL  2.0 µg/mL  4.0 µg/mL  8.0 µg/mL  16 µg/mL
What do you do with an MIC!

Host defenses → Bacteria → Bacterial eradication → Clinical success → Antibiotics

PK/PD profile

You want to have it strong, don't you?
But, what is strong?

Good!!

MIC (µg/ml)

serum concentration
But, what is strong?

**Still Easy...**

**Good !!**

serum concentration

**Bad !!**

MIC (µg/ml)
But, what is strong?

No longer so easy...

serum concentration

MIC (µg/ml)

May be?
Where should the breakpoint be?

- Peak: here?
- No, here!
- Area under the curve
- Trough
- No, there!
Where should the breakpoint be?

- Piperacillin in the US: 64 µg/ml
- Azithromycin in France: 0.25 µg/ml
And there were fierce battles ...
What was THE problem?

- Europe had a number of different breakpoint-setting authorities … and, therefore (?), MANY different breakpoints … *

- In the U.S.A., the NCCLS defined the breakpoints, but those were not (always) rational and realistic, and, in any case, were always linked to the US situation (posologies, modes of administration, type of resistance, etc…)

* having no national breakpoint-setting authority to tell them what to do, Belgian microbiologists most often used the NCCLS breakpoints …
One simple example ...

<table>
<thead>
<tr>
<th>cefotaxime vs. <em>E.coli</em></th>
<th>S&lt; / R</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC United Kingdom</td>
<td>2 / &gt;4</td>
</tr>
<tr>
<td>CA-SFM France</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>CRG The Netherlands</td>
<td>4 / &gt;16</td>
</tr>
<tr>
<td>DIN Germany</td>
<td>2 / &gt;16</td>
</tr>
<tr>
<td>NWGA Norway</td>
<td>1 / &gt;32</td>
</tr>
<tr>
<td>SRGA Sweden</td>
<td>0.5 / &gt;2</td>
</tr>
<tr>
<td>NCCLS U.S.A.</td>
<td>8 / &gt;64</td>
</tr>
</tbody>
</table>

Yet, breakpoints were used everyday by clinical microbiology laboratories to advise clinicians about useful antibiotics against the bacteria they are after …
What is EUCAST?
European Committee on Antimicrobial Susceptibility Testing

- formed in 1997
- convened by
  - European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
  - National Breakpoint Committees in Europe
- financed by
  - ESCMID
  - National Breakpoint Committees in Europe
  - DG-SANCO of the European Union (3 year grant from May 2004)
Main objectives of EUCAST

• In Europe
  – to set common breakpoints for surveillance of antimicrobial resistance;
  – to harmonise clinical breakpoints for existing and new antimicrobial drugs;
  – to promote standardisation of methods;
  – to collaborate with groups concerned with antimicrobial susceptibility testing and/or the epidemiology of antimicrobial resistance;
  – to advise European Union Institutions on the technology and interpretation of antimicrobial susceptibility testing;

• In the world
  – to work with other active groups (eg CLSI [formerly NCCLS] ) to achieve international consensus on susceptibility testing;
EUCAST definitions of epidemiological cut off values

Wild type (WT)
- a microorganism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a microorganism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild type microorganisms may or may not respond clinically to antimicrobial treatment.

Microbiological resistance - non-wild type (NWT)
- a microorganism is defined as non-wild type (NWT) for a species by the presence of an acquired or mutational resistance mechanism to the drug in question.
- a microorganism is categorized as non-wild type (NWT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- non-wild type microorganisms may or may not respond clinically to antimicrobial treatment.

Epidemiological cut-off values will NOT be altered by changing circumstances.
Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown. Click on any species in the left hand column to display the data as a bar chart, with EUCAST epidemiological cut-off values and harmonised European clinical breakpoints.
Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database
EUCAST

MIC
Epidemiological cut-off: WT $\leq 0.064$ mg/L

Clinical breakpoints: S $\leq 0.5$ mg/L, R $> 1$ mg/L

6423 observations (9 data sources)
EUCAST wild type MIC distributions and epidemiological cut-off values – methods and data

Origin of MIC data

Each distribution is comprised of aggregated MIC data including individual MIC distributions from

– publications in international journals
– breakpoint committees
– antimicrobial surveillance systems such as EARSS, SENTRY, the Alexander Project
– pharmaceutical companies and susceptibility testing device manufacturers.

Although different methods may be used, results rarely vary by more than one doubling dilution step. In this way the aggregated EUCAST MIC distributions contain the random variation between different investigators and the systematic variation seen between different methods.
Use of EUCAST wild type MIC distributions

The wild type MIC distributions provide

1. reference material for **epidemiological cut-off values** for antimicrobial resistance surveillance

2. an international reference for **calibration of antimicrobial susceptibility testing methods**

3. reference **MIC ranges of wild type organisms** for a wide spectrum of species and antimicrobials

4. reference material for committees involved in decisions on **clinical breakpoints**
(1) To define epidemiological cut-off values
(2) As a template for calibration of methodology (accuracy and imprecision).

"We have defined the result of antimicrobial susceptibility testing!"
EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)
- level of antimicrobial activity associated with a high likelihood of therapeutic success

Clinically Intermediate (I)
- level of antimicrobial activity associated with indeterminate therapeutic effect

Clinically Resistant (R)
- level of antimicrobial activity associated with a high likelihood of therapeutic failure.

A microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system.

Clinical breakpoints may be altered with legitimate changes in circumstances.
Clinical breakpoints are presented as $S \leq x \text{ mg/L}$; $I > x, \leq y \text{ mg/L}$; $R > y \text{ mg/L}$.
EUCAST procedure for setting breakpoints

The next slides describe the EUCAST procedure for harmonising European breakpoints and reach rational values.

All subsequent slides are an example with ciprofloxacin … and, for some points, with levofloxacin…
1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

<table>
<thead>
<tr>
<th>Dosage</th>
<th>National breakpoint committees</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common dose</strong></td>
<td></td>
</tr>
<tr>
<td>500 x 2 oral 400 x 2 iv</td>
<td>500 x 2 oral 200 x 2 iv</td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td>250 x 2 oral 200 x iv</td>
</tr>
<tr>
<td>500 x 2 oral 200 x iv</td>
<td>200-400 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td>500 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td>400 x 2 iv data pending</td>
</tr>
<tr>
<td>500 x 2 oral 400 x 2 iv</td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td>750 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td>500 x 2 oral 400 x 2 iv</td>
<td>data pending 750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td><strong>Maximum dose schedule</strong></td>
<td></td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td>750 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td>750 x 2 oral 400 x 2 iv</td>
<td>data pending 750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td><strong>Available formulations</strong></td>
<td>oral, iv</td>
</tr>
<tr>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
<tr>
<td>oral, iv</td>
<td>oral, iv</td>
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<tr>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
<tr>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
<tr>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
</tbody>
</table>

**Clinical data**

There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonellae* with low-level fluoroquinolone resistance (MIC>0.064 mg/L) EUCAST has suggested that the epidemiological cut off value (S<0.064/R>0.064 mg/L) be used in Salmonellae systemic infections. These strains are best found using a nalidixic acid 30 µg screen disc in routine susceptibility testing.

There is agreement in EUCAST that ciprofloxacin activity against Enterococci and Streptococci, including S.pneumoniae, is insufficient to categorize wild type bacteria “susceptible”.
2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT \leq X \text{ mg/L})

Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms – reference database
EUCAST

Epidemiological cut-off: WT\leq0.064 \text{ mg/L}

MIC
Epidemiological cut-off: WT \leq 0.064 \text{ mg/L}
Clinical breakpoints: S \leq 0.5 \text{ mg/L}, R > 1 \text{ mg/L}

4416 observations (6 data sources)
### 3. Existing national clinical breakpoints are compared

**Ciprofloxacin** was used in this example:

<table>
<thead>
<tr>
<th>Breakpoints prior to harmonisation (mg/L) S&lt; R&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC</td>
</tr>
<tr>
<td>General breakpoints</td>
</tr>
<tr>
<td>Species related breakpoints</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococci</em></td>
</tr>
<tr>
<td>Streptococci</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Enterococci</td>
</tr>
<tr>
<td><em>Haemophilus/Moraxella</em> spp.</td>
</tr>
<tr>
<td>Corynebacteria</td>
</tr>
<tr>
<td><em>N. Meningitidis</em></td>
</tr>
<tr>
<td><em>N. Gonorrhoeae</em></td>
</tr>
<tr>
<td><em>P. Multocida</em></td>
</tr>
<tr>
<td>Anaerobes</td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
</tr>
</tbody>
</table>
4. Pharmacokinetic data are collected and evaluated

Pharmacokinetic data are collected from various sources, particularly data from patients. If the data allow it and if necessary, population pharmacokinetic models are developed.

These are necessary for PK/PD analyses, including Monte Carlo simulations.

5. Pharmacodynamic data are evaluated

The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC, $C_{\text{max}}$/MIC…) resulting in optimal outcome is determined from:

- in vitro data
- animal studies
- clinical trials
- The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated.
Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens.

- **Ciprofloxacin 500 mg q12h oral**
  - MIC mg/L:
    - S = 0.5 mg/L
  - 99% CI: Lower bound
  - Average: Line

- **Levofloxacin 500 mg q24h oral**
  - MIC mg/L:
    - S = 1 mg/L
  - 99% CI: Lower bound
  - Average: Line
5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint.

"Minimum requirement for S-category" is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug."
6. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin

... thus only a breakpoint of 2 mg/L was acceptable with a footnote that this was based on high dose therapy.

Epidemiological cut off: WT<2.0

Splitting the wild type must be avoided to permit reproducible susceptibility testing!
7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments. When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:
   - EUCAST general committee
   - Expert committees (*Neisseria*, Anaerobes, others)
   - Pharmaceutical industry, AST device manufacturers
     - Others via EUCAST website

9. Rationale document prepared and published on website
And here are the results...

### Fluoroquinolones - EUCAST clinical MIC breakpoints

<table>
<thead>
<tr>
<th>Fluoroquinolone²</th>
<th>Enterobacteriaceae³</th>
<th>Pseudomonas⁴</th>
<th>Acinetobacter⁵</th>
<th>Staphylococcus</th>
<th>Enterococcus A,D,C,G</th>
<th>Streptococcus</th>
<th>S.pneumoniae⁴</th>
<th>H.influenzae M. catarrhalis</th>
<th>N. gonorrhoeae</th>
<th>N. menin- gitidis⁴</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints⁴ Sₕ/Rₕ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>RD</td>
<td>0.5/1</td>
<td>1/1⁴</td>
<td>1/1⁵</td>
<td>--</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5⁴</td>
<td>0.03/0.06</td>
<td>0.03/0.06</td>
<td>--</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>RD</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>2/2</td>
<td>1/1⁴</td>
<td>1/1⁴</td>
<td>IE</td>
<td>IE</td>
<td>--</td>
<td>1/2</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>RD</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>0.5/1</td>
<td>--</td>
<td>0.5/0.5⁴</td>
<td>0.5/0.5⁴</td>
<td>IE</td>
<td>IE</td>
<td>--</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>RD</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>RD</td>
<td>0.5/1</td>
<td>--</td>
<td>1/1³</td>
<td>--</td>
<td>--</td>
<td>0.125/4</td>
<td>0.5/0.5⁴</td>
<td>0.12/0.25</td>
<td>IE</td>
<td>--</td>
<td>0.5/1</td>
</tr>
</tbody>
</table>

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. For breakpoints for other fluoroquinolones (eg. pefloxacin and enoxacin) - refer to breakpoints determined by national breakpoint committees.
3. Salmonella spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by Salmonella spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to S typhim but there are also case reports of poor response with other Salmonella species.
4. The SI/breakpoint has been increased from 0.6 to 1 mg/L to avoid diving the wild type MIC distribution. Thus there is no intermediate category for Acinetobacter species
5. Staphylococcus spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
6. Streptococcus pneumoniae - wild type S pneumoniae are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the ID₅₀ breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the SI/breakpoint from 1.0 to 2.0 to avoid diving the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the SI/breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant. *Haemophilus*/Moraxella - fluoroquinolones low-level resistance (ciprofloxacin MIC is of 0.125 - 0.5 mg/L) may occur in H. influenzae. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with H. influenzae.
8. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
RD = Rationale document listing data used for setting EUCAST breakpoints.
Breakpoints available so far or with projected date…

(see next slides for examples)
### Aminoglycosides - EUCAST clinical MIC breakpoints 23 November 2004

<table>
<thead>
<tr>
<th>Aminoglycosides</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas²</th>
<th>Acinetobacter²</th>
<th>Staphylococcus</th>
<th>Enterococcus³</th>
<th>Streptococcus A,B,C,G</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
<th>M. catarrhalis</th>
<th>N. gonorrhoeae</th>
<th>N. meningitidis</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints⁵ S≤R&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>8/16</td>
<td>8/16</td>
<td>8/16</td>
<td>8/16²</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>8/16</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2/4</td>
<td>4/4</td>
<td>4/4</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2/4</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>2/4</td>
<td>4/4</td>
<td>4/4</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2/4</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2/4</td>
<td>4/4</td>
<td>4/4</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2/4</td>
</tr>
</tbody>
</table>

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
2. The S/A breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.
3. Enterococcus spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and beta-lactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e. with gentamicin MIC>128 mg/L.
4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.
5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

---

 Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30 and updated 22 November 2004

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EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-11-23, G Kehlmetz
Oxazolidinones - EUCAST clinical MIC breakpoints  30 April 2004

<table>
<thead>
<tr>
<th>Oxazolidinone</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas</th>
<th>Acinetobacter</th>
<th>Staphylococcus²</th>
<th>Enterococcus⁴</th>
<th>Staphylococcus A,B,C,G</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
<th>M. catarrhalis</th>
<th>N. gonorrhoeae</th>
<th>N. meningitidis</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>4/4</td>
<td>4/4</td>
<td>2/4</td>
<td>2/4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2/4</td>
</tr>
</tbody>
</table>

1. The S/R-breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild type MIC-distributions. Hence there is no intermediate category.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with – or IE in the table).

- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-11-23, G Kahlmeter
### Cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Enterobacteriaceae²</th>
<th>Pseudomonas³</th>
<th>Acinetobacter⁴</th>
<th>Staphylococcus⁴</th>
<th>Entero-coccus⁴</th>
<th>Streptococcus⁴</th>
<th>Strep.-coccus⁴</th>
<th>S.pneumoniae⁴</th>
<th>H.influenzae⁴</th>
<th>M.catarrhalis⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>RD</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>note⁴</td>
<td>--</td>
<td>--</td>
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<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cefepime</td>
<td>RD</td>
<td>1/8</td>
<td>8/8</td>
<td>--</td>
<td>note⁴</td>
<td>--</td>
<td>--</td>
<td>0.5/0.5⁶</td>
<td>1/2</td>
<td>0.25/0.2⁶</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>RD</td>
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<td>--</td>
<td>--</td>
<td>note⁴</td>
<td>--</td>
<td>--</td>
<td>0.5/0.5⁶</td>
<td>0.5/2⁶</td>
<td>0.12/0.1⁶</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>RD</td>
<td>1/8</td>
<td>8/8</td>
<td>--</td>
<td>--</td>
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<tr>
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<td>RD</td>
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<td>--</td>
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<td>0.5/0.5⁶</td>
<td>0.5/2⁶</td>
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<td>--</td>
<td>note⁴</td>
<td>--</td>
<td>--</td>
<td>0.5/0.5⁶</td>
<td>0.5/1</td>
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</tbody>
</table>

### Notes

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamas in Enterobacteraeaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

3. For ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.

4. Susceptibility of staphylococci to cephalosporins is inferred from the meticillin susceptibility (except cefazidime which should not be used for staphylococcal infections).

5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteraeaceae. To avoid this, the S/I breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and Klebsiella spp only.

6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

---

RD = rationale document listing data used by EUCAST for determining breakpoints.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

---

15-01-2007 Breakpoints - Destelbergen
## Carbapenems - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.1)

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Enterobacteriaceae</th>
<th>Pseudo-monas</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Enterococcus</th>
<th>Strepococcus A,C,D,G</th>
<th>S.pneumoniae</th>
<th>H.influenzae</th>
<th>M.catarrhalis</th>
<th>N.gonorhoeae</th>
<th>N.meningitdis</th>
<th>Gram-negative anaerobes</th>
<th>Non species related breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>RD</td>
<td>0.51</td>
<td>--</td>
<td>--</td>
<td>none</td>
<td>0.5/0.5 A,7</td>
<td>0.5/0.5 A,7</td>
<td>0.5/0.5 A,7</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>1/1</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>RD</td>
<td>0.26</td>
<td>4/6</td>
<td>2/8</td>
<td>none</td>
<td>2/4 A,7</td>
<td>2/2 A,7</td>
<td>2/2 A,7</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>2/8</td>
<td>2/6</td>
</tr>
<tr>
<td>Meropenem</td>
<td>RD</td>
<td>0.28</td>
<td>2/8</td>
<td>2/8</td>
<td>none</td>
<td>2/2 A,7</td>
<td>2/2 A,7</td>
<td>2/2 A,7</td>
<td>IE</td>
<td>0.25/0.25 A,7</td>
<td>2/8</td>
<td>2/8</td>
<td>2/6</td>
</tr>
</tbody>
</table>

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. Proteus and Morganella species are considered poor targets for Imipenem.
3. Susceptibility of Staphylococcus to carbapenems is inferred from the methicillin susceptibility.
4. Imipenem and ertapenem are not used for meningitis. Meropenem breakpoints for Streptococcus pneumoniae and Haemophilus influenzae in meningitis are 0.25/1 mg/L.
5. Meropenem breakpoints in Neisseria meningitidis relates to meningitis only.
6. The Imipenem SI breakpoint for Pseudomonas and Enterococcus was increased from 2 to 4 mg/L to avoid dividing the wild type MIC distribution.
7. Strains with MIC values above the SI breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
8. The ertapenem SI breakpoint for Gram-negative anaerobes was moved from 0.5 to 1.0 to avoid dividing the wild type MIC distributions.

- -- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug
- IE = There is insufficient evidence that the species in question is a good target for therapy with the drug
- RD = Ratescale document listing data used for setting EUCAST breakpoints.

### Version* | Date | Action
---|---|---
1.1 | 2006-06-20 | This table rearranged in reverse chronological order
1.0 | 2005-03-31 | Released by EUCAST

*The number before the point indicates breakpoint change. The number after the point indicates minor changes (footnotes, spelling, format, etc) without a change of breakpoints.
How to implement EUCAST breakpoints

• The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using the one of the European national systems will gradually adhere to the European breakpoint system.

• Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions (local and national surveillance, EARSS, etc).

• Systems for automated susceptibility testing will soon be set up with EUCAST MIC breakpoints.

• Through an agreement between EMEA, EFPIA and EUCAST new antimicrobials will be given breakpoints through EUCAST as part of the registration process. The SPC for these drugs will contain only EUCAST breakpoints.
EMEA – ISAP SOP

European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST

Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST

PUBLIC

<table>
<thead>
<tr>
<th>Prepared by</th>
<th>Approved by</th>
<th>Authorised for issue by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: Bo Aronsson</td>
<td>Name: Agnès Saint Raymond</td>
<td>Name: Patrick Le Courtois</td>
</tr>
<tr>
<td>Signature: On file</td>
<td>Signature: On file</td>
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<tr>
<td>Date: 10 Feb 05</td>
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</table>

Document no.: SOP/H/3043

Effective Date: 14 February 2005

Review Date: 14 February 2007

Supersedes: N/A

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.
Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

- Cephalosporin breakpoints for Enterobacteriaceae
- Carbapenems and Monobactams (!?)

CEN and ISO (EUCAST and CLSI) – international reference method for determination of MICs for non-fastidious bacteria.
EUCAST presentation at CLSI (January 2005, Tampa, Fla)
Will good breakpoints solve everything?

- Breakpoints should only be used as a guidance for the general usage of an existing drug (is it still worth to use it?) or for the positioning of a new drug (has it any chance of being successful?)

- MIC distributions (local and national) must be obtained regularly to check for decreased susceptibilities (epidemiology) and reassessment of posologies and/or therapeutic choices (hospital…)

- Difficult-to-treat patients must be evaluated individually (and MIC obtained …) and questionable drugs must be scrutinized…
Application for an existing pair of drugs in Belgium

% of strains

MIC

0.015 0.03 0.06 0.125 0.25 0.5 1 2 4

0 20 40 60 80 100

Moxi  Levo

moxi  levo

Fluoroquinolone

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>0.125/2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.5/0.5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.125/4</td>
</tr>
</tbody>
</table>

MIC data: J. Verhaegen et al., 2003

6. *Streptococcus pneumoniae* - wild type *S. pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 µg/mL and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
Levofloxacin 500 mg
1X / jr
• AUC [(mg/l)xh] 47
• peak [mg/l] 5
→ MIC_{max} < 0.5

Moxifloxacin 400 mg
1X / jr
• AUC [(mg/l)xh] 48
• peak [mg/l] 4.5
→ MIC_{max} < 0.5

MIC data: J. Verhaegen et al., 2003
A key to success ...

Knowledge or "educated" suspicion of the causative agent

Pathology and epidemiology

Local MIC data

Is the organism probably highly susceptible?

yes

Recommend common dosage with PK/PD ...

no

Suggest to get an MIC

S / I / R is insufficient !!

Recommend dosage adjustment on PK/PD basis
A key to success (follow.) ...

Success?

- no
  - Suggest to re-evaluate
    - the dosage
    - the therapeutic scheme
    - the antibiotic class based on PK/PD properties

- yes
  - This IS time for step-down therapy (if acceptable on a microbiological point of view)

Help clinicians to establish recommendations based on local epidemiology and on the knowledge of the PK/PD properties and of the risk for resistance.