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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What are breakpoints?

- A magic number obtained from *in vitro* susceptibility testing, which the clinical microbiologists use to determine if the antibiotic will or will not be active *in vivo* against a given pathogen;
- This number is usually a given diameter of growth inhibition in an agar plate around a disk loaded with a standard amount of antibiotic;
- While this system gives rise *per definition* to continuous variable (i.e. a diameter of any size [from 0 mm to the limit of the dish…]), microbiologists and authorities like to cut the results into 3 discrete categories:
  - Less than x mm → RESISTANT
  - Larger than y mm → SUSCEPTIBLE
  - Between x and y → INTERMEDIATE

Which is what the clinician will get…

---

1 may be converted into an MIC (see later); automatic machines use growth rates…
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 !!

May be?

Bad !!
Starting from the beginning… The MIC!

Known quantity of bacteria placed into each tube

- 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

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
What do you do with an MIC!

Host defenses

Bacteria

Antibiotics

Bacterial eradication

Clinical success

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

MIC (μg/ml)

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32

serum concentration

$\text{Good !! Easy...}$
But, what is strong?

**MIC (µg/ml)**

<table>
<thead>
<tr>
<th>Serum Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
</tr>
<tr>
<td>0.03</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.12</td>
</tr>
<tr>
<td>0.25</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>32</td>
</tr>
</tbody>
</table>

**Good !!**

**Bad !!**

*serum concentration*
But, what is strong?

No longer so easy...

serum concentration

MIC (µg/ml)

May be?
Where should the breakpoint be?

- Here?
- No, here!
- 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 ≤ / 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 (e.g. 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.
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 ≤ 0.064 mg/L
Clinical breakpoints: S ≤ 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
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!"
If you are above this point, it means that you are non-wild type ... with an acquired resistance mechanism...
But the real question for the clinician is how far above can the bacteria go and still be killed by an antibiotic given to a patient ....
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 \( S < x \text{ mg/L} ; \ I > x, <= y \text{ mg/L} ; \ R > y \text{ mg/L} \)
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>Most common dose</td>
<td></td>
</tr>
<tr>
<td>500 x 2 oral 400 x 2 iv</td>
<td></td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td></td>
</tr>
<tr>
<td>250 x 2 oral 200 x iv</td>
<td></td>
</tr>
<tr>
<td>500 x 2 oral 200 x 2 iv</td>
<td></td>
</tr>
<tr>
<td>200-400 x 2 oral 400 x 2 iv</td>
<td></td>
</tr>
<tr>
<td>500 x 2 oral 400 x 2 iv</td>
<td></td>
</tr>
<tr>
<td>Maximum dose schedule</td>
<td></td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td></td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td></td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td></td>
</tr>
<tr>
<td>750 x 2 oral 400 x 2 iv</td>
<td>data pending</td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td></td>
</tr>
<tr>
<td>Available formulations</td>
<td></td>
</tr>
<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>
<tr>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
<tr>
<td>oral, iv</td>
<td></td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
</tr>
</tbody>
</table>

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})
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>
<th>BSAC</th>
<th>CA-SFM</th>
<th>CRG</th>
<th>DIN</th>
<th>NWGA</th>
<th>SRGA</th>
<th>NCCLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>General breakpoints</td>
<td>ND</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>0.125/2</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>Species related breakpoints</td>
<td>not yet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/1</td>
<td>1/2</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>1/4</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>1/1</td>
<td>1/2</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/1</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.06/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Streptococci</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/2</td>
<td>excl</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>2/2 (I)*</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2 (I)*</td>
<td>0.12/2 (I)*</td>
<td>excl</td>
</tr>
<tr>
<td>Enterococci</td>
<td>excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus/Moraxella spp.</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/0.5</td>
<td>0.12/0.25</td>
<td>1/-</td>
</tr>
<tr>
<td>Corynebacteria</td>
<td>excl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. Meningitidis</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.06/0.12</td>
<td>0.03/0.25</td>
<td></td>
</tr>
<tr>
<td>N. Gonorrhoeae</td>
<td>0.06/-</td>
<td>0.06/1</td>
<td></td>
<td></td>
<td>0.06/0.12</td>
<td>0.06/0.25</td>
<td>0.06/0.5</td>
</tr>
<tr>
<td>P. Multocida</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>0.12/0.25</td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>excluded</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>excluded</td>
<td></td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>2/2</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</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, \(C_{\text{max}}/\text{MIC}\)…) 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
- S = 0.5 mg/L

- Levofoxacin 500 mg q24h oral
- S = 1 mg/L

PK/PD breakpoint calculations are conducted based on conventional dosing regimens.
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>Fluoroquinolone</th>
<th>Pseudo-monas²</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Entero-coccus</th>
<th>Streptococcus</th>
<th>S. pneumonia²</th>
<th>H. influenzae</th>
<th>N. gonorrhoeae</th>
<th>N. meningitidis²</th>
<th>Gram-negative aerobic²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>0.5/1</td>
<td>0.5/1</td>
<td>1/1</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5</td>
<td>0.03/0.06</td>
<td>--</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>--</td>
<td>1/2</td>
<td>2/2</td>
<td>1/1</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>0.5/0.5</td>
<td>0.5/0.5</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>1/1³</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>1/1³</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</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. Typhimurium* but there are also case reports of poor response with other *Salmonella* species.
4. The S/A breakpoint has been increased from 0.5 to 1 mg/L to avoid dividing 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 V8 breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/A breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the S/A 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>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.

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22-05-2007 Breakpoints - Montigny-le-
Breakpoints available so far or with projected date...

(see next slides for examples)

Clinical breakpoints
- Penicillins (2007)
- Cephalosporins
- Carbapenems
- Monobactams
- Fluoroquinolones
- Aminoglycosides
- Glycopeptides
- Oxazolidones
- Macrolides, ketolides & clindamycin, dalfopristine/-quinopristine (2007/08),
- Tetracyclines (2008), Tigecycline
- Chloramphenicol (2008), Daptomycin
- Fusidic acid (2008), Rifampicin (2008)
- Trimethoprim, sulfamethoxazole, co-trimoxazole (2008), Nitrofurantoin (2008)
### Aminoglycosides - EUCAST clinical MIC breakpoints 23 November 2004

<table>
<thead>
<tr>
<th>Aminoglycosides</th>
<th><strong>Enterobacteriaceae</strong></th>
<th><strong>Pseudomonas</strong></th>
<th><strong>Acinetobacter</strong></th>
<th><strong>Staphylococcus</strong></th>
<th><strong>Enterococcus</strong></th>
<th><strong>Streptococcus A,B,C,G</strong></th>
<th><strong>S. pneumoniae</strong></th>
<th><strong>H. influenzae</strong></th>
<th><strong>M. catarrhalis</strong></th>
<th><strong>N. gonorrhoeae</strong></th>
<th><strong>N. meningitidis</strong></th>
<th><strong>Gram-negative anaerobes</strong></th>
<th><strong>Non-species related breakpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>8/16</td>
<td>8/16</td>
<td>8/16</td>
<td>8/16</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>8/16</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2/14</td>
<td>4/14</td>
<td>4/4</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2/4</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>2/14</td>
<td>4/4</td>
<td>4/4</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
<td>2/4</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2/14</td>
<td>4/4</td>
<td>4/4</td>
<td>1/1</td>
<td>--</td>
<td>--</td>
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<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. Entercoccus 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

**EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)**

Updated 2004-11-23, G Kehlmeier
Oxazolidinones - EUCAST clinical MIC breakpoints  30 April 2004

| Oxazolidinone | Enterobacteriaceae | Pseudomonas | Acinetobacter | Staphylococcus | Enterococcus A,B,C,G | Streptococcus | S. pneumoniae | H. influenzae | M. catarrhalis | N. gonorrhoeae | N. meningitidis | Gram-negative anaerobes | Non-species related breakpoints
|---------------|---------------------|-------------|---------------|----------------|---------------------|--------------|--------------|--------------|----------------|----------------|----------------|--------------------------|-----------------
| **Linezolid** | --                  | --          | --            | 4/4            | 4/4                 | 2/4          | 2/4          | --           | --             | --             | --             | --                       | 2/4              |

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
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-lactamases in Enterobacteriaceae. 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 and ceftriaxone 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 methicillin susceptibility (except ceftazidime 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 Enterobacteriaceae. 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 poor target for therapy with the drug.

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
### Carbapenems - EUCAST clinical MIC breakpoints

**2006-06-20 (v 1.1)**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftazidime</strong></td>
<td>RD</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>note³</td>
<td>0.5/0.5</td>
<td>A,7</td>
<td>0.5/0.3</td>
<td>A,7</td>
<td>IE</td>
<td>--</td>
<td>1/1²</td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td>RD</td>
<td>2/8²</td>
<td>4/6</td>
<td>2/8</td>
<td>note³</td>
<td>2/2</td>
<td>4,7</td>
<td>2/2</td>
<td>4,7</td>
<td>IE</td>
<td>--</td>
<td>2/8</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>RD</td>
<td>2/8</td>
<td>2/8</td>
<td>2/8</td>
<td>note³</td>
<td>2/2</td>
<td>4,7</td>
<td>2/2</td>
<td>4,7</td>
<td>IE</td>
<td>0.25/0.25</td>
<td>2/8</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 staphylococci to carbapenems is inferred from the methicillin susceptibility.

4. Imipenem and meropenem 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* refers to meningococci only.

6. The imipenem S/M 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 S/M 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 etaperpenem S/M breakpoint for Gram-negative anaerobes was moved from 0.5 to 1.0 to avoid dividing the wild type MIC distributions.

---

<table>
<thead>
<tr>
<th>Version*</th>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>2006-06-20</td>
<td>This table rearranged in reverse chronological order</td>
</tr>
<tr>
<td>1.0</td>
<td>2005-03-31</td>
<td>Released by EUCAST</td>
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</tbody>
</table>

*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.*
Can we have access to the rationale?

Tigecycline - EUCAST clinical MIC breakpoints 2006-03-30 (v 1.2)

<table>
<thead>
<tr>
<th>Tigecycline (RD)</th>
<th>Species-related breakpoints (S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>En tero bac ter i aceae</td>
<td>Pseudomonas</td>
</tr>
<tr>
<td>1/2.5</td>
<td>–</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 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. Tigecycline has decreased activity against Morganella, Proteus and Providencia.
3. Strains with MIC values above the S/R 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 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 not be reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, PK/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/R and UR breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/R breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = 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.
Can we have access to the rationale?

**Tigecycline - EUCAST clinical MIC breakpoints**  
*2006-03-30 (v 1.2)*

<table>
<thead>
<tr>
<th>Species related breakpoints (S/R)</th>
<th>Enterobacteriaceae</th>
<th>Pseudo-monae</th>
<th>Acinetobacter</th>
<th>Staphylococcius</th>
<th>Enterococcus</th>
<th>Streptococcus</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>
</tr>
</thead>
<tbody>
<tr>
<td>Tigecycline (RD)</td>
<td>1/2/4</td>
<td>--</td>
<td>1E</td>
<td>0.5/0.5/0.5E</td>
<td>0.25/0.25/0.25</td>
<td>0.25/0.25</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>Note*</td>
</tr>
</tbody>
</table>

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1. Non-species related breakpoints: if a given species-specific breakpoint has been published for a particular drug, the species-specific breakpoint should be used. If no species-specific breakpoint is available, the non-species related breakpoint, normally a set of MIC breakpoints that are independent of MIC distributions of specific species, should be used. They are intended for use only for species that have not been tested for resistance to the drug. Species-specific breakpoints are not recommended (marked with -- or IE in the table).

2. Tigecycline has decreased activity against Enterobacteriaceae. Therefore, breakpoints are based on clinical outcome and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is resistant (MIC > 2 mg/L), the isolate is classified as resistant. If the result is sensitive (MIC < 2 mg/L) the isolate is classified as susceptible but no correlation between MIC values, PK/PD data and clinical outcome. Therefore no breakpoint for Enterobacteriaceae can be set.

3. Since the breakpoints have been calculated using MIC endpoints, there is no information about the pharmacokinetics and pharmacodynamics of the drug. Therefore, no breakpoint for Enterobacteriaceae can be set.

4. For anaerobic bacteria there is no published susceptibility testing guideline. So susceptibility testing is given as "susceptible".

5. The S1 and U1 breakpoints are set based on the recommended breakpoints for S. aureus and E. coli.

6. The S1 breakpoint was increased from the S1 breakpoint recommended by the EUCAST.

---

*RD = Rationale document listing data used for setting EUCAST breakpoints*
Can we have access to the rationale?

Tigecycline - EUCAST clinical MIC breakpoints

<table>
<thead>
<tr>
<th>Tigecycline (RD)</th>
<th>Species-related breakpoints (S/R -&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td></td>
<td>1/2*2.5</td>
</tr>
</tbody>
</table>

1. Non-species related breakpoints have been given a species-specific value where appropriate.
2. Tigecycline has decreased susceptibility to 
3. Strains with MIC values above the breakpoint have confirmed the isolate to be resistant.
4. For anaerobic bacteria testing is given in the susceptibility testing is given.
5. The SN and UR breakpoints were increased.
6. The SN breakpoint was increased.

**RD** = Rationale document listing data used for

---

**Introduction**

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation, and has a large volume of distribution. Nausea is the most noteworthy adverse event.

Tigecycline is licensed for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci, β-haemolytic streptococci, enterococci, E. coli, Klebsiella spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.
Can we have access to the rationale?

6. Monte Carlo simulations and Pk/Pd breakpoints

Figure 3 shows the probability of target attainment for *E. coli*. The target is taken from the clinical study on and complicated intra-abdominal infection. The use of this target in the Monte Carlo simulations suggests a Pk/Pd breakpoint of ≤ 0.25 mg/L. Similarly, for Gram-positives simulations suggest a Pk/Pd breakpoint of ≤ 0.25 mg/L using the target of 12.5 obtained from the clinical cSSSI study (data not shown).

Figure 3. Probabilities of target attainment for tigecycline: Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file. Wyeth Inc.
You need to understand the rationale

<table>
<thead>
<tr>
<th>Tigecycline - EUCAST clinical MIC breakpoints</th>
<th>2006-03-30 (v 1.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tigecycline</strong></td>
<td><strong>Species-related breakpoints (S/C/R)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Enterobacteriaceae</strong></td>
</tr>
<tr>
<td><strong>Tigecycline (RD)</strong></td>
<td>1/2</td>
</tr>
</tbody>
</table>

1. Non-species related breakpoints have been determined mainly on the basis of Pla/Pdr data and are independent of MIC distributions of specific species. They are for use only for species that have 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. Tigecycline has decreased activity against Morganella, Proteus and Providencia.
3. 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 confirms 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.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pla/Pdr data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and UR breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = 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.
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.
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

<table>
<thead>
<tr>
<th>PUBLIC</th>
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<tbody>
<tr>
<td>Prepared by</td>
</tr>
<tr>
<td>Name: Bo Aronsson</td>
</tr>
<tr>
<td>Signature: On file</td>
</tr>
<tr>
<td>Date: 10 Feb 05</td>
</tr>
</tbody>
</table>

1. **Purpose**

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.
The future of EUCAST breakpoints

• Are now the official breakpoints for all new drugs and for all new resubmissions to the EMEA

• Will be implemented for diagnostic in 2007-2008 (manufacturers already offer adaptations for customers requesting them)

• May become future International Standards
Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

Done...

- 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)
But is NCCLS (now CLSI…) still authorized to define breakpoints?
The (doomed) future of NCCLS (CLSI) breakpoints

- Over the last 2 years, FDA has reasserted its legal rights to define official breakpoints (and removed if from NCCLS, hence its change of name)

- CLSI may set breakpoints after FDA has defined them, but will NOT publish them if they are different from those of the FDA... (CLSI may petition the FDA for breakpoint revision after 2 years...)

- CLSI will try to become the specialized committee of the FDA for setting breakpoints ... But FDA may not accept this...

- In the meantime, only FDA breakpoints will be legal ... and will be essentially geared to the protection of the American Public

- Other countries will have no direct impact on the FDA-decision process ... and may, therefore, look for another, more "non-national" body for advice and orientation ... This may be CLSI ... or EUCAST...

communicated at General meeting of EUCAST during the 17th ECCMID & 25th ICC (Munich, Germany) by the CLSI representative
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 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 mg/L 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.
My personal view…

Levofloxacin 500 mg  
1X / jr  
• AUC [(mg/l)xh] 47  
• peak [mg/l] 5  
→ MIC$_{\text{max}}$ < 0.5

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

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

Pathology and epidemiology

Knowledge or "educated" suspicion of the causative agent

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