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

and some personal thinking…

Paul M. Tulkens
Representative of ISC to EUCAST (2006 - )
Former member of the EUCAST steering committee (2008-2010)
Member of the European PK/PD of Antinfectives Study Group

Unité de pharmacologie cellulaire et moléculaire
Université catholique de Louvain (UCL), Bruxelles

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

With the support of Wallonie-Bruxelles International

Bach Mai Hospital, Hanoi, Vietnam – 15 April 2011
Towards Rational International Antibiotic Breakpoints: Actions from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and some personal thinking…

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All slides will be (soon) available on http://www.facm.ucl.ac.be
Look for "Advanced Courses"

Bach Mai Hospital, Hanoi, Vietnam – 15 April 2011
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 \(^1\) of growth inhibition in an agar plate around a disk loaded with a standard amount of antibiotic;

• while this system give 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 it in 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 !!

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!

Bacteria → Host defenses

Antibiotics

Bacterial eradication

Clinical success

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

Good!!

serum concentration

MIC (µg/ml)

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32
But, what is strong?

**Still Easy...**

**Good !!**

**Bad !!**

MIC (µg/ml)

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

serum concentration
But, what is strong?

No longer so easy...

MIC (µg/ml)

serum concentration

May be?
If you do not believe me…

MIC distribution of *P. aeruginosa* in Louvain, Belgium

J. van Eldere, 2003
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 6 national breakpoint-setting authorities … and, therefore (?), possibly up to 6 different breakpoints for each antibiotic – bug combination …

• The situation was not better in many other parts of the world …
A simple example …

<table>
<thead>
<tr>
<th>Cefotaxime vs. E. coli</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>
</tbody>
</table>

Yet, these breakpoints were used everyday by clinical microbiology laboratories to advise clinicians about which antibiotic(s) they could successfully use against the bacteria they were supposed to fight …
So, what should "Other" countries do?

Countries without national breakpoint authorities did not really know which one to follow for guidance...
So, what should other countries do?

Do you really need this antibiotic?

2 / >4

4 / >32

2 / >16
So, what if you are small?
but [hopefully]) smart …

The "filet américain" attitude *

* baguette filet américain 100% boeuf
A simple decision ...

Now, the clinician can treat all patients

Was this not smart decision?

<table>
<thead>
<tr>
<th></th>
<th>U.S.A.</th>
<th>NCCLS / CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>&gt; 64</td>
</tr>
</tbody>
</table>

\[
\text{CEFOTAXIME vs. E. coli}\\
\text{BSAC (UK) 2 / > 4}\\
\text{CA-SFM (France) 4 / > 32}\\
\text{CRG (Netherlands) 4 / > 16}\\
\text{DIN (Germany) 2 / > 16}\\
\text{NWGA (Norway) 1 / > 32}\\
\text{SRGA (Sweden) 0.5 / > 2}\\
\text{NCCLS / CLSI (US) 8 / > 64}\\
\]
The pros and cons of using CLSI breakpoints

Pros

• Readily available for most antibiotics
• Based on evaluation of molecules by an independent committee acting very scientifically and clinically…
• Backed by an extensive set of guidelines and recommendations for testing…
• Used widely and considered as 'gold standard' in most publications and surveillance networks…
• Subject to periodic revisions to remain in line with the evolution of science, including PK/PD and increase of resistance
The pros and cons of using CLSI breakpoints

Cons

• You need to pay for …
• Limited access of non-US persons to the decision process …
• Decisions based on proposals made by Industry…
• Guidelines and recommendations for testing not necessarily applicable specifically where you are…
• Antibiotics not registered for use in the US may not be included and/or fully studied
• Revision process not always as effective as it could be…
• For certain antibiotics, CLSI breakpoints have been notoriously too high
The pros and cons of using CLSI breakpoints

Cons

• You need to pay for …
• Limited access of non-US persons to the decision process …
• **Decisions based on proposals made by Industry…**
• Guidelines and recommendations for testing not necessarily applicable specifically where you are…
• Antibiotics not registered for use in the US may not be included and/or fully studied
• Revision process not always as effective as it could be…
• For certain antibiotics, **CLSI breakpoints have been notoriously too high**

simple "cause to effect" relationship
An example of (probably) too high CLSI breakpoints

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage¹</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit</th>
<th>Breakpoints (mg/L)²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>Efficacy b</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\text{AUC}_{24\text{h}}$ (mg $\times$ h/L)</td>
<td></td>
<td>of resistance c</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>0.1–0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Ciprofloxin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>0.2–0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>0.3–0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Levofloxin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>0.3–0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Moxifloxin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>0.2–0.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

¹ NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncclpga)

² NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncclpga)

An unanticipated problem …
(if you are a non-US microbiologist)
An unanticipated problem …

• Since 2006, FDA has reasserted its legal rights to define official breakpoints.

• CLSI may determine and publish breakpoints no sooner than 24 months after FDA decision (and only if the company requests this [?]).

• In the meantime, only FDA breakpoints will be legal in the US, and will be essentially geared to the protection of the US Public for drugs registered in the US.

• Non-US organizations have no direct possibility to impact on the FDA-decision process …

communicated at the General meeting of EUCAST during the 17th ECCMID & 25th ICC (Munich, Germany) by the CLSI representative.
Two important change in Europe…

1. Each national committee in EU (UK, FR, NL, DE, SV, NO) has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision taken in 2008 should be into their systems in January 2009, and so on …

In parallel, (i) the manufacturers of devices (BM and BD) have both said that it is realistic that their machines will have EUCAST breakpoints in 2010; (ii) interpretative criteria for disk-based assay have been fully released by EUCAST in 2010
Two important change in Europe...

2. EMEA and EUCAST have set up an agreement that makes EUCAST responsible for defining breakpoints for new molecules proposed for registration in Europe.

EUCAST breakpoints will be accepted by EMEA and put into the "Summary of Product Characteristics", which is part of legal documents accompanying the marketing authorization in EU.
### Doripénème: concentrations critiques

Les concentrations minimales inhibitrices (CMI) critiques établies par l’European Committee on Antimicrobial Susceptibility Testing (EUCAST) sont les suivantes:

<table>
<thead>
<tr>
<th>Concentration critique</th>
<th>S ≤1 mg/L et R &gt;4 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non liée à l’espèce</strong></td>
<td>déduite de la sensibilité à la méticilline</td>
</tr>
<tr>
<td>Staphylocoques</td>
<td></td>
</tr>
</tbody>
</table>

**Enterobacteriaceae**

<table>
<thead>
<tr>
<th>Concentration critique</th>
<th>S ≤1 mg/L et R &gt;4 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td></td>
</tr>
<tr>
<td>autres que S. pneumoniae</td>
<td>S ≤1 mg/L et R &gt;1 mg/L</td>
</tr>
</tbody>
</table>

**S. pneumoniae**

<table>
<thead>
<tr>
<th>Concentration critique</th>
<th>S ≤1 mg/L et R &gt;1 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entérocoques</td>
<td></td>
</tr>
</tbody>
</table>

**Haemophilus spp.**

<table>
<thead>
<tr>
<th>Concentration critique</th>
<th>S ≤1 mg/L et R &gt;1 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td>Anaérobies</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** pour les Anaérobies, les données insuffisantes pour déterminer la CMI critique.
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.
Antimicrobial wild type distributions of microorganisms

- Search database

MIC- and Inhibition zone diameter distributions of microorganisms without and with resistance mechanisms
Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown.

http://www.eucast.org/mic_distributions/
Click on any antibiotic (or 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)
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!"
Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST

If you are above this point, it means that you are non-wild type ... with an acquired resistance mechanism...

MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L
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 $S \leq x \text{ mg/L} ; \ I >x, < y \text{ mg/L} ; \ R >y \text{ mg/L}$
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 levofloxacine…
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>500 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td></td>
<td>500 x 2 oral 200 x 2 iv</td>
</tr>
<tr>
<td></td>
<td>250 x 2 oral 200 x 2 iv</td>
</tr>
<tr>
<td></td>
<td>500 x 2 oral 200 x 2 iv</td>
</tr>
<tr>
<td></td>
<td>200-400 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td></td>
<td>500 x 2 oral 400 x 2 iv</td>
</tr>
<tr>
<td>Maximum dose schedule</td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td></td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td></td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td></td>
<td>750 x 2 oral 400 x 3 iv</td>
</tr>
<tr>
<td></td>
<td>data pending</td>
</tr>
<tr>
<td>Available formulations</td>
<td>oral, iv</td>
</tr>
<tr>
<td></td>
<td>oral, iv</td>
</tr>
<tr>
<td></td>
<td>oral, iv</td>
</tr>
<tr>
<td></td>
<td>oral, iv</td>
</tr>
<tr>
<td></td>
<td>oral, iv</td>
</tr>
<tr>
<td></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 ≤ X mg/L)
### 3. Existing national clinical breakpoints are compared

*Ciprofloxacin* was used in this example:

<table>
<thead>
<tr>
<th></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><strong>General breakpoints</strong></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><strong>Species related breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1/1</td>
<td>0.12/2</td>
<td>0.12/1</td>
<td>1/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>1/4</td>
<td>ND</td>
<td>1/1</td>
<td>1/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td></td>
<td>1/1</td>
<td>1/2</td>
<td>1/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td>1/1</td>
<td>0.12/2</td>
<td>0.06/2</td>
<td>1/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>1/1</td>
<td>0.12/2</td>
<td>0.12/2</td>
<td>excl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>2/2 (I)*</td>
<td>excluded</td>
<td>0.12/2 (I)*</td>
<td>0.12/2 (I)*</td>
<td>excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td>excluded</td>
<td>excluded</td>
<td>0.12/2</td>
<td>0.12/2</td>
<td>1/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus/Moraxella</em> spp.</td>
<td>1/1</td>
<td></td>
<td>0.12/0.5</td>
<td>0.12/0.25</td>
<td>1/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corynebacteria</td>
<td></td>
<td>excl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>N. Meningitidis</em></td>
<td>1/1</td>
<td>0.06/0.12</td>
<td>0.03/0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>N. Gonorrhoeae</em></td>
<td>0.06/-</td>
<td>0.06/1</td>
<td>0.06/0.12</td>
<td>0.06/0.25</td>
<td>0.06/0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. Multocida</em></td>
<td>ND</td>
<td>ND</td>
<td>0.12/0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>excluded</td>
<td>ND</td>
<td>excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.</td>
<td>1/1</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>2/2</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></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: 0.25, 0.5, 1, 2, 4, 8
  - fAUC/MIC vs MIC mg/L graph
  - S = 0.5 mg/L

- **Levofloxacin 500 mg q24h oral**
  - MIC mg/L: 0.25, 0.5, 1, 2, 4, 8
  - fAUC/MIC vs MIC mg/L graph
  - S = 1 mg/L
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
Clinical breakpoints

Clinical breakpoints are free and available for everyday use in the clinical laboratory to advise on patient therapy.

In EUCAST tables, the I-category is not listed. It is implied as the values between the S-breakpoint and the R-breakpoint.

For a breakpoint listed as S<=1 mg/L and R>8 mg/L, the intermediate category is 2-8 (technically >1-8) mg/L.

For a breakpoint listed as S>=22 mm and R<18 mm, the intermediate category is 18-21 mm.
And here are the results… (April 2011)

Enterobacteriaceae

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin¹</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Nalidixic acid (screen)</td>
<td>Note²</td>
<td>Note²</td>
<td>30</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacain</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

These are much lower than the CLSI (current) breakpoints which are between 1 – 2 – 4 (ciprofloxacin) en 2 – 4 – 8 (ofloxacin)

but compare now with the PK/PD breakpoints ...
### PK/PD breakpoints for fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage(^a)</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (µg/ml) for Efficacy(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(C_{\text{max}}) in mg/L total/free (dose)</td>
<td>(\text{AUC}_{24\ h}) total/free</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
</tr>
<tr>
<td>Ofloxacain</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
</tr>
</tbody>
</table>

---

\(^a\) Typical daily dosage

1. Efficacy refers to the upper limit of sensitivity (µg/ml) for each drug.

---

Enterobacteriaceae

<table>
<thead>
<tr>
<th>Carbapenems</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (μg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Doripenem</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Imipenem²</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

• The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases).

• Some strains that produce carbapenemase are categorized as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorization of susceptibility.

• In many areas, carbapenemase detection and characterization is recommended or mandatory for infection control purposes.
### EUCAST and cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporins</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1</td>
<td>2</td>
<td>30</td>
</tr>
</tbody>
</table>

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.
P. aeruginosa in Europe between 1997 and 2005

In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou¹, Sylviane Carbonnelle², Laëtitia Avrain³,⁴, Narcisa Mesaros³,⁵, Jean-Paul Pirnay⁶, Florence Bilocq⁶, Daniel De Vos⁷,⁸, Anne Simon⁹, Denis Piérard⁵, Frédérique Jacobs⁸, Anne Dediste⁹, Paul M. Tulkens¹,⁴, Françoise Van Bambeke¹, Youri Glupczynski¹

Supported by the
- "Région Bruxelloise/Brusselse Gewest" (Research in Brussels)
- FNRS (post-doctoral fellowships)
- FRSM
**P. aeruginosa in Brussels in 2007-2009**

![Graphs showing the cumulative percentage of MIC values for various antibiotics including amikacin, ciprofloxacin, meropenem, piperacillin/tazobactam, cefepime, and ceftazidime. The x-axis represents MIC values in mg/L, ranging from 0.0156 to 512 mg/L, while the y-axis represents the cumulative percentage. The graph indicates the EUCAST and CLSI breakpoints.](image-url)

**Legend:**
- **EUCAST bkpt > R**
- **CLSI bkpt ≥ R**
Can we have access to the rationale?

### Enterobacteriaceae

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S \leq R &gt;</td>
<td></td>
<td>S \geq R &lt;</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Minocycline</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tigecycline(^1)</td>
<td>1 2</td>
<td>15</td>
<td>18(^A) 15(^A)</td>
</tr>
</tbody>
</table>

[http://www.srga.org/eucastwt/MICTAB/RD/tigecyclinerationale1.0.pdf](http://www.srga.org/eucastwt/MICTAB/RD/tigecyclinerationale1.0.pdf)
Can we have access to the rationale?

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>Tetracyclines</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S ≤</td>
<td>R ≥</td>
<td>S ≥</td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Minocycline</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>1</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

Introduction
Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycycle. 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 licenced 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).

These isolates WILL create a risk of failure.
But then why $S \leq 1$ and $R > 2$?

**Enterobacteriaceae**

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>MIC breakpoint (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$S \leq$</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>-</td>
</tr>
<tr>
<td>Minocycline</td>
<td>-</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>-</td>
</tr>
<tr>
<td>Tigecycline$^1$</td>
<td>1</td>
</tr>
</tbody>
</table>

- The Pk/Pd breakpoint of 0.25-0.5 cuts within the wild type population
- Clinical success was obtained up to 1-2 mg/L (from clinical trials)
- BUT remember
  - the risk will increase > 0.5 mg/L
  - tigecycline is intrinsically an antibiotic with a small margin for efficacy …
- you must monitor resistance based on MIC
Why could (should ?) non-EU countries follow EUCAST breakpoints?

Pros
• The procedure is rational and transparent
• All proposals are subject to open discussions through the web site and/or by direct contact
• All breakpoints and the supporting material ("rational documents") is available free on the web site for inspection and analysis *
• Adaptation to local conditions can, therefore, be made seamlessly if needed (changes in dosages, PK, resistance patterns…)

Cons
• There is no specific procedure for requesting and implementing changes based on national realities outside of EU *
• Material must be submitted by the organization requesting a breakpoint.

* except via country representatives (see www.eucast.org), ISC (me) or FESCI (Dr D. Livermore)
Will good (EUCAST ?) breakpoints solve everything ?

- Breakpoints should only be used as a guidance for a 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 …)
A key to success ...

Knowledge or "educated" suspicion of the causative agent → Local MIC data

Pathology and epidemiology

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
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

A key to success (follow.) ...
Useful web sites…

- [http://www.eucast.org](http://www.eucast.org)
  - breakpoints and rational documents
  - SPCs and European Assessment report
- [http://www.facm.ucl.ac.be](http://www.facm.ucl.ac.be)
  - This lecture and many others