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
Unité de pharmacologie cellulaire et moléculaire
Université catholique de Louvain, Bruxelles

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

Liège, Belgium
14 November 2006
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. Lawyers like you to be guilty or innocent …

4. 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

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
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

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

Good!! Easy...

MIC (µg/ml)

serum concentration
But, what is strong?

Good!!

serum concentration

Bad!!
But, what is strong?

No longer so easy...

serum concentration

MIC (µg/ml)

May be?
Where should the breakpoint be?

- peak
- area under the curve
- trough

- 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 (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 \text{ mg/L}

Clinical breakpoints: S \leq 0.5 \text{ mg/L}, \ R > 1 \text{ 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.
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>250 x 2 oral 200 x 2 iv</td>
<td>500 x 2 oral 200 x 2 iv</td>
</tr>
<tr>
<td>200-400 x 2 oral 400 x 2 iv</td>
<td>500 x 2 oral 400 x 2 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 3 iv</td>
</tr>
<tr>
<td>data pending</td>
<td></td>
</tr>
<tr>
<td>750 x 2 oral 400 x 3 iv</td>
<td></td>
</tr>
<tr>
<td><strong>Available formulations</strong></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>
</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”.

---

14-11-2006 Breakpoints - Liège

---