EUCAST breakpoints

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Bruxelles, Belgium

Based (largely) on presentations available from the EUCAST Web site, given to me by Gunnar Kahlmeter, or borrowed from Johan Mouton and Derek Brown
But before that, where are you from?

Belgium

The medical campus of the Université catholique de Louvain

The Cellular and Molecular Pharmacology Group

slides are available on www.facm.ucl.ac.be \( \rightarrow \) Lectures
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 \(\rightarrow\) RESISTANT
  – larger than \(y\) mm \(\rightarrow\) SUSCEPTIBLE
  – between \(x\) and \(y\) \(\rightarrow\) INTERMEDIATE

which is what the clinician will get…

\(^1\) may be converted into an MIC (see later); automatic machines use growth rates…
But, what is susceptible?

MIC (µg/ml)

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

serum concentration

Good !! Easy...

Beirut, Lebanon, 3 February 2012
Lebanese Society for Infectious Diseases and Clinical Microbiology
But, what is resistant?

**Good !!**

**Bad !!**

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>Serum Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>Good</td>
</tr>
<tr>
<td>0.03</td>
<td>Good</td>
</tr>
<tr>
<td>0.06</td>
<td>Good</td>
</tr>
<tr>
<td>0.12</td>
<td>Good</td>
</tr>
<tr>
<td>0.25</td>
<td>Good</td>
</tr>
<tr>
<td>0.5</td>
<td>Good</td>
</tr>
<tr>
<td>1</td>
<td>Good</td>
</tr>
<tr>
<td>2</td>
<td>Bad</td>
</tr>
<tr>
<td>4</td>
<td>Bad</td>
</tr>
<tr>
<td>8</td>
<td>Bad</td>
</tr>
<tr>
<td>16</td>
<td>Bad</td>
</tr>
<tr>
<td>32</td>
<td>Bad</td>
</tr>
</tbody>
</table>
And what do you do with this?

No longer so easy...

serum concentration

May be?
If you do not believe me…

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

A graph showing the MIC distribution of *P. aeruginosa* in Louvain, Belgium, for fluoroquinolones. The graph includes the MIC values for ofloxacin (oflox), levofloxacin (levo), and ciprofloxacin (cipro) at different concentrations.

J. van Eldere, 2003
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 ...
A simple example …

<table>
<thead>
<tr>
<th>cefotaxime vs. <em>E. coli</em></th>
<th>$S \leq / R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC United Kingdom</td>
<td>2 / $\geq 4$</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 if you are "another country"?

but [hopefully]) smart …
So, what if you are "another country"?  
but [hopefully]) smart ...
A simple decision ...

Now, the clinician can treat all patients

| NCCLS / CLSI | U.S.A. | 8 / > 64 |

Was this not smart decision?
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 …
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• Limited access of non-US persons to the decision process …
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• 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
An example of (probably) too high CLSI breakpoints

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit</th>
<th>Breakpoints (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>14/11</td>
<td>Efficacy 0.1–0.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>24/18</td>
<td>Efficacy 0.2–0.8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>40/30</td>
<td>Efficacy 0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>40/28</td>
<td>Efficacy 0.3–0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>35/21</td>
<td>Efficacy 0.2–0.7</td>
</tr>
</tbody>
</table>

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

An unanticipated problem since 2006 ...  
(if you are a non-US microbiologist)
An unanticipated problem since 2006...

- 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 changes 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 changes 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.
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; renewed and put under the umbrella of the E-CDC since 2008)
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.

http://www.eucast.org/mic_distributions/
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**
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 $S < x \text{ mg/L} ; I > x, < y \text{ mg/L} ; R > y \text{ mg/L}$
Clinical breakpoints should tell us which MIC above the epidemiological cut-off treatment will be effective ...
EUCAST procedure for setting breakpoints

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

All subsequent slides are an example with ciprofloxacin … and, for some points, with levofloxacin…
EUCAST method of determining clinical breakpoints

1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT \textless{}X mg/L)

3. Comparison is made between available breakpoints (for already registered antibiotics)
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, \( \frac{C_{\text{max}}}{\text{MIC}} \)) 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.

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**ciprofloxacin 500 mg q12h oral**

- *S* = 0.5 mg/L

**levofloxacin 500 mg q24h oral**

- *S* = 1 mg/L

---

**Pharmacokinetic/Pharmacodynamic (PK/PD) Breakpoint**

<table>
<thead>
<tr>
<th>MIC mg/L</th>
<th>ciprofloxacin 500 mg q12h oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIC mg/L</th>
<th>levofloxacin 500 mg q24h oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

---

**99% CI**

- Average

---

**MIC mg/L**

- 0.25
- 0.5
- 1
- 2
- 4
- 8

---

**AUC/MIC**

- 0
- 20
- 40
- 60
- 80
- 100
- 120
- 140
- 160
- 180
- 200
EUCAST method of determining clinical breakpoints

5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint.

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.
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 (<i>Neisseria</i>, Anaerobes, others)
   - Pharmaceutical industry, AST device manufacturers
   - Others via EUCAST website

9. Rationale document prepared and published on website
The next slides describe the EUCAST procedure for harmonising European breakpoints and reach rational values.

EUCAST breakpoints are freely available.

Clinical breakpoints

Clinical breakpoints are 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 $S < 1 \text{ mgL}$ and $R > 8 \text{ mgL}$, the intermediate category is $2 \cdot 8$ (technically $1 \cdot 8$) mgL.

For a breakpoint listed as $S = 22 \text{ mm}$ and $R < 18 \text{ mm}$, the intermediate category is $18 \cdot 21 \text{ mm}$.

EUCAST breakpoints are freely available

Clinical breakpoints - bacteria (v 1.1) - pdf-file for printing (April 27, 2010)
Clinical breakpoints - bacteria (v 1.1) - Excel-file for screen (April 27, 2010)
Clinical breakpoints - fungi (MIC breakpoints)
Definitions of clinical breakpoints and epidemiological cut off values
Procedure for harmonizing and defining breakpoints

Recommend page
And here are the results… *(April 2011)*

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<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></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>
<td>22</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Nalidixic acid (screen)</td>
<td>Note²</td>
<td>Note²</td>
<td>30</td>
<td>16ᴬ</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
<td>22</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</th>
<th>Typical PK values (mg/L total/free dose)</th>
<th>Proposed PK/PD upper limit of sensitivity (µg/ml) for efficacy</th>
<th>EUCAST breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>0.1–0.4</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>0.2–0.8</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>0.3–0.9</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>0.3–0.9</td>
<td>1-2</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>0.2–0.7</td>
<td>0.5–1</td>
</tr>
</tbody>
</table>

EUCAST breakpoints

References:
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.

---

**Why so low?**

**To exclude ESBL...**
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 ≤</td>
<td>R &gt;</td>
<td>S ≥</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</td>
<td>1</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

Is the methodology available?

EUCAST disk diffusion test for routine antimicrobial susceptibility testing

During 2009 - 2010 EUCAST is developing a disk diffusion test for routine antimicrobial susceptibility testing. ESCMID has decided to take responsibility for the development and upkeep of the EUCAST disk diffusion test over the next several years.

The method is derived from the Kirby-Bauer method, variants of which are currently widely used in Europe, but is calibrated to EUCAST MIC breakpoints.

The method is based on two media, Mueller-Hinton agar without supplements (MH) for non-fastidious organisms, including enterococci, and MH with 5% horse blood and 20 mg L-NAD (MH-L) for Streptococcus spp. including Streptococcus pneumoniae, Haemophilus spp. and other fastidious organisms.

The plates are incubated at 35°C ± 1°C for 18 ± 2 h within 15 minutes from application of the disks. MH plates are incubated in air and MH-L plates in 5% CO2.

Breakpoint tables with tentative zone diameter breakpoints were published December 31, 2009.

http://www.eucast.org/eucast_disk_diffusion_test/
Can we have access to the zone diameter values?

You will find the disk diffusion value for all antibiotics.
And what about manufacturers (plates and/or automated systems)

EUCAST breakpoints and commercially available material and systems for AST - important information to laboratories (updated 2010-03-16). CLICK here.

The preparedness of manufacturers of AST materials (media, plates, disks) and AST systems - click here for the latest information (26 January, 2012).

**Preparedness of Manufacturers offering materials and automated systems for EUCAST susceptibility testing**

- Based on questionnaires to manufacturers of materials and systems for antimicrobial susceptibility testing.

- The tables will be updated when manufacturers report changes in their preparedness (contact erika.matuschek@ltkronoberg.se).

Last updated 2012-01-26

**Disk/plates:**
- most are ready

**ATS**
- Phoenix: OK
- Microscan: +/-
- bdMérieux: --
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 (http://www.eucast.org)
• Adaptation to local conditions can, therefore, be made seamlessly if needed (changes in dosages, PK, resistance patterns…).
Why could (should ?) non-EU countries follow EUCAST breakpoints ?

**Cons 🙁**

- Adopting EUCAST breakpoints will require a re-thinking about resistance levels and their significance *
- There is no specific procedure for requesting and implementing changes based on national realities outside of EU **
- Starting material must be submitted by the organization requesting a breakpoint.

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* two typical example are the R breakpoints for (i) penicillin and *S. pneumoniae* (almost all isolates are "S" since the new CLSI breakpoint…), and (ii) vancomycin and *S. aureus* (CLSI breakpoint of ≥ 8 m/L will classify VISA as intermediate … which they are not !; see next slide).

** except via country representatives (see www.eucast.org), ISC (me) or FESCI (Dr D. Livermore)
Discrepancies EUCAST – CLSI: an example...

Vancomycin breakpoints for S. aureus

This is where the VISA strains are
Will good (EUCAST ?) 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 dosing and/or therapeutic choices (hospital…)

• Difficult-to-treat patients must be evaluated individually (and MIC obtained …)
Useful web sites…

- **http://www.eucast.org**
  - breakpoints and rational documents
- **http://www.ema.europa.eu**
  - SPCs and European Assessment report
- **http://www.facm.ucl.ac.be**
  - This lecture and many others