EUCAST breakpoints

Paul M. Tulkens
Representative of ISC to EUCAST (2006 - )
Member of the EUCAST steering committee (2008-2010)

Co-Founder and Past-President of the
International Society of Anti-infective Pharmacology (ISAP)

Member of the ESCMID PK/PD of Anti-Infectives Study Group (EPASG)

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute
Université catholique de Louvain (UCL)
Bruxelles, Belgium

Based (largely) on presentations available from the EUCAST Web site,
given to me by Gunnar Kahlmeter and other members of EUCAST steering committee
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 yields *per definition* a *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 \(\Rightarrow\) RESISTANT
  - Larger than y mm \(\Rightarrow\) SUSCEPTIBLE
  - Between x and y \(\Rightarrow\) INTERMEDIATE

This is what the clinician will get…

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

**Easy**

Good!!

serum concentration

MIC (µg/ml)

31 May 2012

ISP - WIV, Brussels, Belgium
But, what is resistant?

Good!!

Serum concentration

Bad!!

MIC (µg/ml)
And what do you do with this?

No longer so easy...

serum concentration

May be?
If you do not believe me...

MIC distribution of clarithromycin for *S. pneumoniae* from confirmed clinical cases of CAP in Belgium (2004-2009; n=239; 7 hospitals)

Susceptibility is largely a "yes/no" situation (an accurate breakpoint value is relatively unimportant)

"wild type" population

Lismond et al., IJAA 2012; 39:208-216
If you do not believe me...

MIC distribution of piperacillin-tazobactam for *P. aeruginosa* from confirmed clinical HAP in Belgium (2005-2009; n=90; 5 hospitals)

The population spreads over a wide range of MIC values. A correct breakpoint is critical.

"wild type" population

Data from Riou et al. IJAA (2010) 36:513-522
Presented as by Lismond et al., IJAA 2012; 39:208-216
Another example from Belgium…

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

- Oflox (blue diamonds)
- Levo (pink squares)
- Cipro (yellow triangles)

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 in Europe…

From Mouton, 8th ISAP symposium, Nijmegen, 2001
A simple example of European diversity...

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

The "filet américaain" attitude *

* baguette with raw chopped 100% pure beef
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 must pay for …
• Limited access to the decision process for non-US persons …
• 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 to the decision process for non-US persons …
• 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 dosage(^{a})</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit</th>
<th>Breakpoints (mg/L)(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(C_{\text{max}}) in mg/L total/free (dose)</td>
<td>(\text{AUC}_{24\text{h}}) (mg × h/L) total/free</td>
<td>Efficacy(^{b})</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
<td>0.1–0.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
<td>0.2–0.7</td>
</tr>
</tbody>
</table>

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

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 (ECoff)

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.
The European Committee on Antimicrobial Susceptibility Testing - EUCAST
EUCAST MIC distributions

MIC distributions

Link to the website with MIC distributions
Antimicrobial wild type distributions of microorganisms

- Search database

MIC- and Inhibition zone diameter distributions of microorganisms without and with resistance mechanisms

MIC distributions

The website gives MIC distributions for individual organisms and antimicrobial agents in tables and histograms. The distributions are based on collated data from an increasing total of more than 20,000 MIC distributions from worldwide sources. Unless otherwise specifically stated, the data are representative of results obtained with a variety of MIC methods. Different methods do not necessarily give equivalent results.
**EUCAST MIC distributions**

**Antimicrobial wild type distributions of microorganisms**

Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown...
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.
Read the epidemiological cut-off

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

16702 observations (55 data sources)
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L
The epidemiological cut-off is set by extrapolation.

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

---

**Ciprofloxacin / Escherichia coli**

**EUCAST MIC Distribution - Reference Database 2012-05-26**

MIC: 0.002 - 0.5 mg/L

Epidemiological cut-off: WT ≤ 0.064 mg/L

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

16702 observations (55 data sources)
Use of EUCAST wild type MIC distributions and epidemiological cut-off

The wild type MIC distributions provide

1. reference material 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
Moving to clinical breakpoints …

which is what the clinician will get… *

But why not giving her / him an MIC ?
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 $S \leq x \text{ mg/L} ; \ I > x, \leq y \text{ mg/L} ; \ R > y \text{ mg/L}$
Clinical breakpoints should tell to 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 ≤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, 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**

**levofloxacin 500 mg q24h oral**

\[ S = 0.5 \text{ mg/L} \]

\[ S = 1 \text{ mg/L} \]
EUCAST method of determining clinical breakpoints

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

This part is critical and relates mainly to "CART" analyses (to which MIC can you go with still good clinical success?)

"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.

**Important caveat for new drugs**
Minimum requirement and tigecycline as an example

The S breakpoint is at the limit of the highest value of the wild type distribution that also corresponds to the limit of the PK/PD target attainment rate.
EUCAST method of determining clinical breakpoints

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
The levofloxacin dilemma ...

Levofloxacin / Streptococcus pneumoniae
EUCAST MIC Distribution - Reference Database 2012-05-26

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

But the PK/PD breakpoint for 500 mg/day is 1

Epidemiological cut off is 2

Splitting the wild type must be avoided to permit reproducible susceptibility testing!

... thus the breakpoint was moved to 2 mg/L with a footnote that this was based on high dose therapy.

MIC
Epidemiological cut-off: WT ≤ 2 mg/L
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

85464 observations (17 data sources)
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
EUCAST breakpoints are freely available

The European Committee on Antimicrobial Susceptibility Testing - EUCAST
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 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<16 mm the intermediate category is 16-21 mm.

- Clinical breakpoints - bacteria (v 2.0) - pdf file for printing (2012-01-01)
- Clinical breakpoints - bacteria (v 2.0) - Excel file for screen (2012-01-01)
  A new set of tables for antibacterials were uploaded on Feb 23, 2012, only because all links to MIC distributions were updated because the database was moved.
- Clinical breakpoints - fungi (v 4.1) - Excel file for screen (2012-03-15)
- Clinical breakpoints - fungi (v 4.1) - pdf file for printing (2012-03-15)
  A new set of tables for antifungals were uploaded on March 15, 2012, because of changes in caspofungin ("IE" changed to "Note 3").
And here are the results…

<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>16²</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(^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>Norfloxacin</td>
<td>800 mg</td>
<td>C(_{\text{max}}) in mg/L total/free (dose)</td>
<td>14/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AUC(_{24\text{h}}) (mg × h/L) total/free</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4/1.1 (400 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td></td>
<td>24/18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5/1.75 (500 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td></td>
<td>40/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/3 (400 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td></td>
<td>40/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/2.8 (500 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td></td>
<td>35/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1/1.8 (400 mg PO)</td>
<td></td>
</tr>
</tbody>
</table>

---

\(^a\)EUCAST breakpoints

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 &lt;</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.
Discrepancies EUCAST – CLSI: an example…

Vancomycin breakpoints for *S. aureus*

This is where the VISA strains are!!
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 ≤ R &gt;</td>
<td>S ≥ R &lt;</td>
<td></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>Tigecycline¹</td>
<td>1</td>
<td>15</td>
<td>18² 15²</td>
</tr>
</tbody>
</table>

http://www.srga.org/eucastwt/MICTAB/RD/tigecyclinerationale1.0.pdf
What methodology do you need to use?

- You should have an MIC…
  - Set your system to get one!
    - Microdilution (ISO method)
    - E-test (calibrate!)
    - Automatic system (not all are good…)

- But we know many labs still work with disks…
  - Any disk methodology can be used if you have the correlation table for values around S – R limits
    - BSAC, CA-SFM … or even CLSI (but …)
    - EUCAST sisk diffusion methodology
EUCAST susceptibility testing recommendations

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing is performed with phenotypic or genotypic methods. The basis of phenotypic methods is the minimum inhibitory concentration (MIC). Clinical MIC breakpoints determine whether the organism is categorized as susceptible, intermediate or resistant to the agent in question. Other methods should be calibrated to reference MIC methods.

Users of EUCAST breakpoints should use the EUCAST disk diffusion method or other susceptibility testing systems calibrated to EUCAST breakpoints and terminology in accordance with EUCAST breakpoint tables. For more information - CLICK here.

- **Disk diffusion methodology**
  Detailed description of the EUCAST disk diffusion test
- **Disk diffusion implementation**
  Guidance documents on how to implement the disk diffusion test
- **Compliance of manufacturers**

And what about manufacturers (plates and/or automated systems)

Compliance of manufacturers

Compliance of manufacturers of susceptibility testing products with EUCAST recommendations

Preparedness of manufacturers of susceptibility testing devices and materials (updated 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: --
EUCAST breakpoints in Europe in 2011

% Laboratories
- >50%
- 10-50%
- <10%
- No information 2012

[Map showing EUCAST breakpoints in Europe with color-coded regions indicating % of laboratories meeting certain thresholds.]
EUCAST and EMA

breakpoints for new drugs with EMA

• Daptomycin  ✓
• Tigecycline  ✓
• Doripenem ✓
• Telavancin ✓
• Glycopeptides (one ongoing)
• Cephalosporins (activity against MRSA - ongoing)
• Anti-MTB (one - two agents - ongoing)
An example: doripenem (DORIBAX)

Bijsluiter voor het publiek

DORIBAX 500 mg poeder voor oplossing voor infusie

Samenvatting van de kenmerken van het product (SKP)

DORIBAX 500 mg poeder voor oplossing voor infusie

http://www.fagg-afmps.be/nl/
An example: doripenem (DORIBAX)

NAAM VAN HET GENEESMIDDEL

Doribax 500 mg poeder voor oplossing voor infusie
(JANSSEN-CILAG)

Drempelwaarden
Drempelwaarden voor de Minimale Inhiberende Concentratie (MIC), vastgesteld door het European Committee on Antimicrobial Susceptibility Testing (EUCAST) zijn als volgt:

<table>
<thead>
<tr>
<th>Species/Genus</th>
<th>MIC Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stafylokokken</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 4 \text{mg/l}$</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>afgeleid uit de drempelwaarde van methicilline</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 4 \text{mg/l}$</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 4 \text{mg/l}$</td>
</tr>
<tr>
<td>Streptococcus spp. behalve S. pneumoniae</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 1 \text{mg/l}$</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 1 \text{mg/l}$</td>
</tr>
<tr>
<td>Enterokokken</td>
<td>‘ongeschikt doel’</td>
</tr>
<tr>
<td>Haemophilus spp.</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 1 \text{mg/l}$</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>onvoldoende bewijs</td>
</tr>
<tr>
<td>Anaeroben</td>
<td>$S \leq 1 \text{mg/l en } R &gt; 1 \text{mg/l}$</td>
</tr>
</tbody>
</table>
EUCAST at the corner of your street

Countries are encouraged to form National AST Committees (NAC).

- Antimicrobial susceptibility testing
  - Strategy at national level
  - Implementation of breakpoints and methods
  - Education (national workshops, websites)
  - Liaison and consultation with EUCAST (chairman or scientific secretary GC representative)
  - Liaison with groups involved in AMR-surveillance (ECDC, EARSS, ...)
  - QA
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 dosing and/or therapeutic choices (hospital…)

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

• [http://www.eucast.org](http://www.eucast.org)
  – breakpoints and rational documents
  – SPCs and European Assessment reports
• [http://www.facom.ucl.ac.be](http://www.facom.ucl.ac.be)
  – This lecture and many others