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

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
But before that, where are you from?

Belgium

Brussels

The medical campus of the Université catholique de Louvain

The Cellular and Molecular Pharmacology Group

slides are available on www.facm.ucl.ac.be ➔ 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?

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 resistant?

Still Easy...

Good !!

serum concentration

Bad !!

MIC (µg/ml)

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

J. van Eldere, 2003
Where should the breakpoint be?

- peak: here?
- trough: NO, here!
- area under the curve: 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><strong>cefotaxime vs. <em>E. coli</em></strong></th>
<th><strong>S ≤ / R</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC</td>
<td>2 / &gt;4</td>
</tr>
<tr>
<td>CA-SFM</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>CRG</td>
<td>4 / &gt;16</td>
</tr>
<tr>
<td>DIN</td>
<td>2 / &gt;16</td>
</tr>
<tr>
<td>NWGA</td>
<td>1 / &gt;32</td>
</tr>
<tr>
<td>SRGA</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 ...

The "filet américain" attitude *

* baguette with raw chopped 100% pure beef
A simple decision …

Now, the clinician can treat all patients

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

Was this not a 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 …
• 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
# 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></td>
<td></td>
<td>$C_{max}$ in mg/L</td>
<td>$AUC_{24,h}$ (mg × h/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>total/free</td>
<td>total/free</td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(dose)</td>
<td></td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of resistance</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.ncc

---

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 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.

---

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST

Document no.: SOP/H/3043

Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST

Effective Date: 14 February 2005

Review Date: 14 February 2007

Supersedes: N/A

PUBLIC

Prepared by

Approved by

Authorised for issue by

Name: Bo Arousso

Name: Agnès Saint Raymond

Name: Patrick Le Courtois

Signature: On file

Signature: On file

Signature: On file

Date: 10 Feb 05

Date: 10 Feb 05

Date: 10 Feb 05

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

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 $S \leq x \text{ mg/L}; \ I > x, \leq y \text{ mg/L}; \ R > y \text{ mg/L}$.
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 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 \( \leq X \) 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.
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 (Neisseria, 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.
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>Ofloxacin</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>
<th>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>AUC$_{24\ h}$ (mg x h/L) total/free</td>
<td>0.1–0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
<td></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>

EUCAST breakpoints: 0.5-1

---

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.
### Cephalosporins

<table>
<thead>
<tr>
<th></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></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.
Can we have access to the rationale?

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetracyclines</strong></td>
</tr>
<tr>
<td>MIC breakpoint (mg/L)</td>
</tr>
<tr>
<td>S ≤</td>
</tr>
<tr>
<td>Doxycycline</td>
</tr>
<tr>
<td>Minocycline</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
<tr>
<td>Tigecycline¹</td>
</tr>
</tbody>
</table>

http://www.srga.org/eucastwt/MICTAB/RD/tigecyclinerationale1.0.pdf
Can we have access to the methodology for disks?

EUCAST Disk Diffusion Test

EUCAST has developed a European disk (not tablet) diffusion test based on MH-agar and disks from several manufacturers for non-fastidious organisms and on MH-agar with 5% defibrinated horse blood and 20 mg/L beta-NAD (MH-F) for fastidious microorganisms (streptococci, H.influenzae and others). Tentative breakpoints were published on the 21st of December, 2009.

Manufacturers of disks, tablets, media and automated AST systems are working to calibrate their products to the EUCAST standards. Some are ready while others are still facing difficulties. Users of European breakpoints are advised to consult with EUCAST before choosing AST systems alternative to:

1. MIC-determination using European breakpoints
2. European disk test method calibrated to European breakpoints
3. Automated susceptibility testing with a machine validated for use with European breakpoints.
Can we have access to the methodology for disks?

EUCAST Disk Diffusion Test

EUCAST has developed a European disk (not tablet) diffusion test based on MH-agar and disks from several manufacturers for non-fastidious organisms and on MH-agar with 5% defibrinated horse blood and 20 mg/L beta-NAD (MH-F) for fastidious microorganisms (streptococci, H.influenzae and others). Tentative breakpoints were published on the 21st of December, 2009.

Manufacturers of disks, tablets, media and automated AST systems are working to calibrate their products to the EUCAST disk diffusion test, others are still facing difficulties to do so.

Check list for implementation of EUCAST Susceptibility Testing

1. MIC-determination using EUCAST disks
2. European disk test method
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

http://www.eucast.org
Can we have access to the methodology for disks?

EUCAST Disk Diffusion Test

EUCAST has developed a European disk (not tablet) diffusion test based on MH-agar and disks from several manufacturers for non-fastidious organisms and on MH-agar with 5% defibrinated horse blood and 20 mg/L beta-NAD (MH-F) for fastidious microorganisms (TM). Tentative breakpoints were published on September 2009.

Manufacturers of disks, tablets, media and devices need to calibrate their products to the EUCAST breakpoints. Others are still facing difficulties. Users are advised to consult with EUCAST before choosing:
1. MIC-determination using European breakpoint tables
2. European disk test method calibrated with EUCAST
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

- Preparation of media for disk diffusion
- EUCAST Disk Diffusion - Manual (v. 1.0 Dec 18, 2009)
- EUCAST Disk Diffusion - Slide Show (v. 1.1 Jun 3, 2010)
- EUCAST Disk Diffusion - Reading Guide (v. 1.0 Apr 30, 2010)

http://www.eucast.org
Can we have access to the methodology for disks?

EUCAST Disk Diffusion

EUCAST has developed a European methodology for determining MIC on MH-agar and disks from several manufacturers, and on MH-agar with 5% defibrinated sheep blood (MH-F) for fastidious microorganisms. Tentative breakpoints were published in 2008. More recent breakpoints were published in 2011.

Manufacturers of disks, tablets, and powders have started to calibrate their products to the European guidelines. Some others are still facing difficulties. Please consult with EUCAST before choosing a disk manufacturer.

1. MIC-determination using European disks
2. European disk test method calibrated to European breakpoints
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

Clinical breakpoint tables v 1.3 (2011-01-05) - for printing
Clinical breakpoint tables v 1.3 (2011-01-05) - for screen
List of errata in EUCAST tables (update 2011-05-05)

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

**Antimicrobial wild type distributions of microorganisms**

**Search**

- Method: Disk diffusion
- Antimicrobial: Ciprofloxacin (Method: Disk diffusion)

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

You will find the disk diffusion value for all antibiotics.
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 *
• Starting 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 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 report
- [http://www.facm.ucl.ac.be](http://www.facm.ucl.ac.be)
  - This lecture and many others