MIC breakpoints – the reference for routine susceptibility testing methods

Gunnar Kahlmeter

ECCMID 2010
# Breakpoint committees
for determining clinical MIC breakpoints

<table>
<thead>
<tr>
<th>Committee</th>
<th>Country</th>
<th>Disk test?</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC</td>
<td>United Kingdom</td>
<td>Yes</td>
</tr>
<tr>
<td>CA-SFM</td>
<td>France</td>
<td>Yes</td>
</tr>
<tr>
<td>CLSI</td>
<td>USA</td>
<td>Yes</td>
</tr>
<tr>
<td>CRG</td>
<td>The Netherlands</td>
<td>No</td>
</tr>
<tr>
<td>DIN</td>
<td>Germany</td>
<td>No</td>
</tr>
<tr>
<td>NWGA</td>
<td>Norway</td>
<td>No</td>
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<tr>
<td>SRGA</td>
<td>Sweden</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Breakpoint committees

EUCAST (Europe)
- BSAC wp on AST (UK)
- CA-SFM (F)
- CRG (NL)
- DIN (D)
- NWGA (N)
- SRGA (S)

CLSI (USA)
EUCAST General Committee
All European Countries + ISC/FESCI

EUCAST Steering Committee
BSAC, CA-SFM, CRG, DIN, NWGA, SRGA
And 2 reps from the General Committee

Subcommittees
Antifungals
Anaerobes
Expert Rules

National Breakpoint Committees
D, F, N, NL, S, UK,
**Steering Committee and General Committee**

- **General Committee**
  - Each European country invited to appoint one representative each
  - ISC and FESCI one rep each
  - One meeting per year; mail consultation

- **Steering Committee (11 members)**
  - Chairman, Scientific Secretary and Clinical Data Coordinator appointed by ESCMID
  - Each national breakpoint committee 1 rep
  - General Committee 2 reps
  - 5 meetings per year
  - Appointments by ESCMID (5) and National Breakpoint committees (6)
It is now time to implement EUCAST breakpoints in European countries.

This workshop will discuss various aspects of susceptibility testing in general …and the EUCAST breakpoint system and methodology in particular …and how to implement it in routine laboratories.
EUCAST Tasks

1. **Determine clinical breakpoints for existing and new antibacterials, antifungals, antimycobacterials (ESCMID, EMEA, ECDC).**

2. **Define wild type MIC distributions and epidemiological cut-off values for bacteria and fungi.**

3. **Develop susceptibility testing methods and systems for internal QC (ESCMID).**

4. **Liaise with EMEA, ECDC, EFSA, EARSS and others involved in antimicrobial resistance.**

5. **Liaise with national committees involved in antimicrobial resistance and susceptibility testing, to facilitate implementation of European breakpoints.**
Why European breakpoints in Europe?

- based on EMEA approved indications and outcome evaluation, Pk/Pd, multiple MIC distributions, and modern principles of determining breakpoints
- related to European minimum and maximum dosages
- accepted by European regulatory authorities (EMEA, ECDC)
- official breakpoints in European SPCs (EMEA)
- ”case definitions” for antimicrobial resistance surveillance (ECDC)
- transparent and published rationale behind decisions
- independent of commercial interests
- reviewed at intervals: with new member of class or on initiative of the profession, EMEA, the Company, EUCAST.
- in the public domain and free of charge
Tools for determining CLINICAL BREAKPOINTS

1. Dose or doses
2. Target organisms
3. MIC-distributions for target organisms without resistance mechanisms
   - breakpoints not to divide MIC-distributions of WT target organisms
   - MIC distribution and ECOFFs determined for each species
4. Resistance mechanisms and corresponding MICs in target organisms
5. Clinical indications
6. Pharmacokinetics (Cmax, AUC, T½, Protein binding, Vd..)
7. Pharmacodynamic properties (peak conc/MIC, AUC/MIC, TA, MCs)
8. Clinical outcome (clinical outcome/MIC)
9. Epidemiological cutoffs, Pk/Pd-breakpoints and clinical data together determine the CLINICAL BREAKPOINT
Methods for susceptibility testing

• **Phenotypic test methods**
  based on antimicrobial activity (MIC) and breakpoints
  – MIC-determination (broth, agar, Etest, M.I.C.E.), disk diffusion (BSAC, CA-SFM, CLSI, SRGA), automated systems (the viteks, phoenixes, microscans)
  – **Predicts susceptibility and resistance**
  – **Quantifiable**

• **Genotypic test methods**
  based on the detection of a resistance gene or its product
  – mecA, vanA, vanB, ….PBP2, … betalactamase detection…. 
  – **Predicts resistance, not sensitivity**
  – **Not quantifiable**

• **By deduction – ”expert rules”**
  – If mecA-positive then report betalactam antibiotics R;
    If ESBL-positive, then report betalactam antibiotics R;
    If erythromycin-resistant, then report roxithro- and clarithromycin R;
  – **Predicts susceptibility and resistance.**
  – **Not quantifiable**
Phenotypic susceptibility testing is based on MIC
Clinical breakpoints and susceptibility testing

- The MIC breakpoint is valid only in a standardised method for phenotypic susceptibility testing.

- The breakpoint is based on the MIC. All other phenotypic methods (disk diffusion, gradient tests, automated phenotypic susceptibility testing etc) are related/calibrated to the MIC.

  Clinical laboratory testing and in vitro diagnostic test systems - Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices –
  Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases.

ISO 20776-2 (2007)
The ECOFF defines the upper end MIC of organisms without resistance!
MICs are relative

– It’s like any 20 chefs in 20 cities in 20 countries - with the same recipee and kitchen tools they can almost make a cacciatora pizza taste the same wherever…..

…but the flour, tomatoes, salami, other ingredients, oven temperature etc will decide the final result.

……but with practise, standardisation and hard work we can almost ”make them absolute”.

Setting breakpoints

• The pharmaceutical company submits for approval a new drug to EMEA (or a national agency in Europe – through the mutual recognition pathway). Relevant parts of the file are sent to the EUCAST Steering Committee (confidentiality clause)

• **EMEA** approves (or not) clinical indications, dosages (min and max), administration forms (oral, iv, infusion etc) and target organisms.

• **EUCAST** decides on breakpoints for organisms approved by EMEA

• An SOP regulates the relationship between EMEA, EUCAST and the Company (www.eucast.org)
1. Decide on target organisms for clinical indications
2. Define the wild type MIC distribution (i.e. of organisms without resistance mechanisms to the drug/class)
3. Decide on the S-, I- or R-categorization of wild type organisms (clinical data, Pk and Pd).
4. Decide on S-, I- and R-categorization of microorganisms with MICs outside the WT distribution

Ciprofloxacin / Escherichia coli
EUCAST MIC Distribution - Reference Database

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

Wild type

MIC
Epidemiological cut-off: WT ≤ 0.032 mg/L
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

17877 observations (82 data sources)
Clinical resistance
Phenotypically detectable resistance
Genetically detectable resistance

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

MIC
Epidemiological cut-off: WT ≤ 0.032 mg/L
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

17877 observations (82 data sources)
The MIC is the reference for all other phenotypic tests.

E coli /Mecillinam 10 ug
969 isolates, of which 930 consecutive

<table>
<thead>
<tr>
<th>Breakpoints</th>
<th>S</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC</td>
<td>≤8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Zone diameter</td>
<td>≥15</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>
EUCAST and existing antimicrobials

- Aminoglycosides ✓
- Carbapenems & aztreonam ✓
- Cephalosporins iv ✓
- Cephalosporins oral ✓
- Fluoroquinolones ✓
- Glycopetides ✓
- Macrolides and lincosamides ✓
- Penicillins ✓
- Tetracyclines ✓
- Miscellaneous antimicrobials ✓
- Antifungal drugs (flu- and voriconzole) ✓
### Topicals and less commonly used drugs

1. Mupirocin (Topical)
2. Polymyxin B (Topical)
3. Bacitracin (Topical)
4. Streptomycin (hlr for enterococci)
5. Neomycin (Topical)
6. Sulfamethoxazole (UTI)
7. Cephalothin (expert rules?)
8. Sulfadiazine
9. Spiramycin
10. Nalidixic acid (screening)
11. Cefoperazone
12. Pefloxacin
13. Cefradine
14. Cefamandole
15. Sulfisoxazole
16. Pipemidic acid
17. Kanamycin
18. Ceftizoxime
19. Cefprozil

+ 45 others
Consult with expert groups

- Neisseria spp (finalised)
- Anaerobes (ESGARAB, ongoing)
- Helicobacter pylori (EHSG, ongoing)
- Clostridium difficile (ESGCD, ongoing)
- Camplylobacter (VetCast, ongoing)
- ...
- ...
- ...
• **Antifungals**
  - Antifungal drugs in need of breakpoints
  - Breakpoints and rationale documents
  - Methods

• **Anaerobe bacteria**
  - Antibiotics in need of breakpoints
  - Breakpoints
  - Methods

• **Expert Rules**
  - Tables of intrinsic resistance
  - Expert rules (IF/THEN)
EUCAST Website

www.eucast.org

free of charge
requires no login
The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMEA and ECDC.

EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control.

The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European countries, ESCMID and ISCL. The Steering Committee also consults experts within the fields of Infectious Diseases and Microbiology, pharmaceutical companies and susceptibility testing device manufacturers on EUCAST protocols.

EUCAST has subcommittees on antifungal susceptibility testing, expert rules for antimicrobial susceptibility testing, and antimicrobial susceptibility testing of anaerobes.

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST by 2009. Breakpoints for new agents are set as part of the licensing process for new agents through EMEA. EUCAST breakpoints will be available in devices for automated susceptibility testing during 2009 and 2010. A disk diffusion test calibrated to EUCAST MIC breakpoints was launched at the end of 2009.

EUCAST invites anyone with an interest in antimicrobial agents in general and antimicrobial breakpoints in particular to contact EUCAST, ESCMID or one of the National Breakpoint Committees.
## EUCAST breakpoint tables

<table>
<thead>
<tr>
<th>MIC (mg/L) brpts*</th>
<th>S ≤ 2  R &gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone (mm) brpts*</td>
<td>S ≥ 22  R &lt; 22</td>
</tr>
<tr>
<td>Insufficient evidence (Literature: &quot;not enough evidence for a breakpoint&quot; or &quot;no indication&quot;)</td>
<td>IE Can not be substituted. Can be supplemented with an MIC without interpretation.</td>
</tr>
<tr>
<td>Inappropriate drug (Literature: poor drug – don’t use!)</td>
<td>— Can be substituted with an automatic &quot;R&quot;.</td>
</tr>
<tr>
<td>Numbered footnotes</td>
<td>MIC-breakpoints</td>
</tr>
<tr>
<td>Lettered footnotes</td>
<td>Zone diameter breakpoints</td>
</tr>
</tbody>
</table>

*when numbers are the same = no intermediate category
## Enterobacteriaceae

### Penicillins

<table>
<thead>
<tr>
<th></th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤ R &gt;</td>
<td>S 2 R &lt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Penicillin</strong></td>
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<tr>
<td>Benzylpenicillin</td>
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<tr>
<td>Ampicillin</td>
<td>Note*</td>
<td>6</td>
<td>10-10</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Ampicillin-sulbactam</td>
<td>Note*</td>
<td>6</td>
<td>10-10</td>
<td></td>
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<tr>
<td>Amoxicillin</td>
<td></td>
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<td></td>
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<tr>
<td>Amoxicillin-clavulanate</td>
<td>Note*</td>
<td>6</td>
<td>20-10</td>
<td></td>
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<tr>
<td>Piperacillin</td>
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<tr>
<td>Pipercillin-tazobactam</td>
<td></td>
<td>6</td>
<td>50-6</td>
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<tr>
<td>Ticarcillin</td>
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<tr>
<td>Ticarcillin-clavulanate</td>
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<td>6</td>
<td>75-10</td>
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<tr>
<td>Phenoxymethylpenicillin</td>
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<td>Oxacillin</td>
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<tr>
<td>Cloxacillin</td>
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<tr>
<td>Dicloxacillin</td>
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<tr>
<td>Fluoxacillin</td>
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<tr>
<td><strong>Ampicillin (uncomplicated UTI only)</strong></td>
<td></td>
<td>6</td>
<td>10</td>
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</table>

### Cephalosporins

<table>
<thead>
<tr>
<th></th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤ R &gt;</td>
<td>S 2 R &lt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefalexin</strong></td>
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<tr>
<td>Cefadroxil</td>
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<td></td>
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<tr>
<td>Cefadroxil (uncomplicated UTI only)</td>
<td></td>
<td>16</td>
<td>30</td>
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<td>Cefalexin</td>
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<tr>
<td>Cefalexin (uncomplicated UTI only)</td>
<td></td>
<td>16</td>
<td>30</td>
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<tr>
<td>Cefazolin</td>
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<td>Cefazolin (uncomplicated UTI only)</td>
<td></td>
<td>16</td>
<td>30</td>
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</table>

### Notes

1. For ampicillin breakpoints, the resistant breakpoint of >6 mg/L ensures that all isolates with resistance mechanisms are reported resistant. The wide range of isolates in this group are often resistant to orally administered ampicillin, with some strains resistant to orally administered ampicillin.

2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate using these breakpoints. For epidemiological or infection control purposes laboratories may want to use a test which specifically screens for the presence of ESBLs.
On a national level:

National strategies and joint decisions on AST are needed!

NAC

National Antimicrobial Committee
National Antimicrobial Committees tasks

- Subcommittee on Antimicrobial susceptibility testing
  - Strategy at national level
  - Implementation of breakpoints and methods
  - Education
  - Liaison and consultation with EUCAST
  - Liaison with groups involved in AMR-surveillance (ECDC, EARSS, ....).
  - QA

- Antimicrobial Policies
- Antimicrobial Resistance Surveillance
- Antimicrobial Consumption and Policies
# EUCAST breakpoints

<table>
<thead>
<tr>
<th>Decisions for 2010/11:</th>
<th>Discussions ongoing:</th>
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<tr>
<td>Sweden</td>
<td>Spain</td>
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<tr>
<td>Denmark</td>
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<td>Wales</td>
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<td>Switzerland</td>
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</table>
ENAC
European Network of Antimicrobial Committees
The EUCAST General Committee.
• Harmonised breakpoints for all major antibacterial and antifungal drugs.
• Orphan drugs and microorganisms identified and prioritized
• Breakpoints for new drugs as part of the approval process with EMEA (daptomycin, tigecycline, doripenem).
• Epidemiological cut off values determined for all drugs.
• SOPs to describe formal relationship with EMEA.
• EUCAST breakpoints mandatory in European SPCs.
• ISO-standardized MIC-determination.
• Software and database for MIC- and zone distributions.
• Breakpoints implemented in national (F, D, N, NL, S, UK) systems 2007 – 2010.
• EUCAST disk diffusion test launched 2009.
• Breakpoint tables, QC-tables, methodology documents available on website.
EUCAST April 2011

- EUCAST disk diffusion method implemented in 5 - 6 countries
- NACs in 10 – 15 countries.
- National Educational Workshops on European AST in several countries.
- EUCAST breakpoints in all major systems for AST (BSAC, CA-SFM; Commercial systems Phoenix, Vitek2, Microscan, BioMic).
- All Rational Documents available on website.
- SOPs to describe formal relationship with ECDC.
- ECDC decided on European breakpoints as mandatory in surveillance of antimicrobial resistance and HCAI.
- Breakpoints and methods for Campylobacter, Helicobacter, C.difficile, and others.
- Breakpoints and methods several topical antimicrobials and several less commonly used drugs.
- Formal decision on the future relationship between EUCAST, ECDC, EMEA and ESCMID.
Thank you!