EUCAST
-standardising antimicrobial susceptibility testing in Europe

Derek Brown

www.EUCAST.org
## European breakpoint committees 1997

<table>
<thead>
<tr>
<th>Committee</th>
<th>Country</th>
<th>Disk diffusion 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>CRG</td>
<td>The Netherlands</td>
<td>No</td>
</tr>
<tr>
<td>DIN</td>
<td>Germany</td>
<td>Yes</td>
</tr>
<tr>
<td>NWGA</td>
<td>Norway</td>
<td>No</td>
</tr>
<tr>
<td>SRGA</td>
<td>Sweden</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Implications of differences between breakpoints in different countries

- Different guidance on appropriate therapy
- Resistance rates may be different in different surveillance studies despite no difference in MIC distribution
EUCAST General Committee
All European Countries + ISC/FESCI

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

Subcommittees
Antifungals
Anaerobes
Expert Rules

National Breakpoint Committees
France, Germany, Netherlands
Norway, Sweden, UK

Consultation with
Expert groups
Industry
EUCAST Steering Committee

- Chairperson: Gunnar Kahlmeter
- Scientific secretary: Derek Brown
- Clinical data coordinator: Rafael Canton

- BSAC (UK): Alasdair MacGowan
- CA-SFM (France): Claude-James Soussy/Luc Dubreuil
- CRG (The Netherlands): Johan Mouton
- DIN (Germany): Arne Rodloff
- NWGA (Norway): Matin Steinbakk/Arnfinn Sundsfjord
- SRGA (Sweden): Christian Giske

- General Committee rep: Marina Ivanova (Estonia)
- General Committee rep: Petra Apfalter (Austria)
  - Previously Czech Republic, Greece, Russia, Spain, Italy, Poland, Finland and ISC
EUCAST General Committee

- One representative, appointed by the appropriate medical associations, from each European country

- One representative each from ISC and FESCI

- Chairperson, Scientific secretary and Clinical Data Coordinator (appointed by ESCMID)

- Meets once a year at ECCMID

- All Steering Committee proposals are referred to the General Committee for comment before decision
EUCAST email networks

- Pharmaceutical companies
- Manufacturers of susceptibility testing devices
- Expert groups and individuals
Setting breakpoints in EUCAST

- Harmonisation of European breakpoints
- Setting breakpoints for new agents (with EMA)
- Review of existing breakpoints
1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

<table>
<thead>
<tr>
<th>Dosage</th>
<th>BSAC UK</th>
<th>CA-SFM France</th>
<th>CRG Netherlands</th>
<th>DIN Germany</th>
<th>NWGA Norway</th>
<th>SRGA Sweden</th>
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</thead>
<tbody>
<tr>
<td>Most common dose</td>
<td>500 x 2 oral</td>
<td>500 x 2 oral</td>
<td>250 x 2 oral</td>
<td>500 x 2 oral</td>
<td>200-400 x 2 oral</td>
<td>500 x 2 oral</td>
</tr>
<tr>
<td></td>
<td>400 x 2 iv</td>
<td>200 x 2 iv</td>
<td>200 x 2 iv</td>
<td>200 x 2 iv</td>
<td>400 x 2 iv</td>
<td>400 x 2 iv</td>
</tr>
<tr>
<td>Maximum dose schedule</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>tbc</td>
<td>750 x 2 oral</td>
</tr>
<tr>
<td></td>
<td>400 x 3 iv</td>
<td>400 x 3 iv</td>
<td>400 x 3 iv</td>
<td>400 x 2 iv</td>
<td></td>
<td>400 x 3 iv</td>
</tr>
<tr>
<td>Available formulations</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
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</table>
2. Existing national clinical breakpoints are compared

<table>
<thead>
<tr>
<th>Breakpoints prior to harmonisation (mg/L) S&lt; R&gt;</th>
<th>BSAC</th>
<th>CA-SFM</th>
<th>CRG</th>
<th>DIN</th>
<th>NWGA</th>
<th>SRGA</th>
<th>CLSI</th>
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</thead>
<tbody>
<tr>
<td><strong>General breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>0.125/2</td>
<td>1/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Species related breakpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/1</td>
<td>1/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>1/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/1</td>
<td>1/2</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/1</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.06/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Streptococci</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/2</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>2/2 (I)*</td>
<td>0.12/2 (I)*</td>
<td>0.12/2 (I)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Haemophilus/Moraxella spp.</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/0.5</td>
<td>0.12/0.25</td>
<td>1/-</td>
</tr>
<tr>
<td>Corynebacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06/0.12</td>
<td>0.03/0.25</td>
<td></td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.06/1</td>
<td>0.06/0.12</td>
<td>0.06/0.25</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>0.06/1</td>
<td></td>
<td></td>
<td></td>
<td>0.06/0.12</td>
<td>0.06/0.25</td>
<td>0.06/0.5</td>
</tr>
<tr>
<td>P. multocida</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.12/0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>2/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Multiple MIC distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values (ECOFF) determined (WT ≤ X mg/L)

Epidemiological cut-off: WT ≤ 0.03 mg/L
4. Using available Pk/Pd data, Monte Carlo simulations are performed and a Pk/Pd breakpoint calculated based on conventional dosing regimens
EUCAST procedure for setting breakpoints

5. Clinical data relating outcome to MIC values, wild type and resistance mechanisms are assessed in relation to the tentative breakpoint
EUCAST procedure for setting breakpoints

6. Tentative breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints.

...the breakpoints were set at $S \leq 0.12$ and $R > 2\ \text{mg/L}$, rendering wild type \textit{S. pneumoniae} intermediate in susceptibility to ciprofloxacin.

Splitting the wild type must be avoided to permit reproducible susceptibility testing.
## EUCAST procedure for setting breakpoints

### 7. Tentative breakpoints proposed 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 groups (eg *Neisseria* spp., anaerobes)
- Pharmaceutical industry, AST device manufacturers
- Others via EUCAST website

### 9. Breakpoint finalised and rationale document prepared and published on website
EUCAST harmonised breakpoints for existing agents

- Aminoglycosides
- Penicillins
- Cephalosporins iv
- Cephalosporins oral
- Carbapenems
- Aztreonam
- Fluoroquinolones
- Glycopeptides
- Macrolides
- Tetracyclines
- Miscellaneous antimicrobials
Topicals and less commonly used drugs

Mupirocin (Topical)
Polymyxin B (Topical)
Bacitracin (Topical)
Streptomycin (HLR enterococci)
Neomycin (Topical)
Sulfamethoxazole (UTI)
Cephalothin (expert rules?)
Sulfadiazine
Spiramycin
Nalidixic acid (screening)

Cefoperazone
Pefloxacin
Cefradine
Cefamandole
Sulfisoxazole
Pipemidic acid
Kanamycin
Ceftizoxime
Cefprozil

+ 45 others
Microorganisms being evaluated for breakpoints

- *Helicobacter* spp.
- *Campylobacter* spp.
- *Clostridium difficile*
- *Legionella* spp.
- *Pasteurella multocida*
- *Listeria monocytogenes*
- *Burkholderia cepacia*
- *Corynebacterium* spp.
Setting breakpoints for new agents

- The pharmaceutical company submits a new antimicrobial agent to **EMA** for approval

- Relevant parts of the file are shared with the EUCAST Steering Committee (confidential process)

- **EMA** 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 EMA
EUCAST breakpoints for new drugs (European Medicines Agency, EMA)

- Daptomycin
- Tigecycline
- Doripenem
- Glycopeptides (ongoing)
- Ceftobiprole (withdrawn)
- Garenoxacin (withdrawn)
- Iclaprim (withdrawn)
Review of breakpoints by EUCAST

- New resistance mechanisms
- New agent in class
- New clinical experience
- Altered indications
- Change in dosing or administration
- Change in target organisms
## EUCAST review of breakpoints 2009 - 2010

<table>
<thead>
<tr>
<th>Agent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Some changed</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Changed</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>No change</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Changed</td>
</tr>
<tr>
<td>Colistin (<em>Pseudomonas</em> spp.)</td>
<td>Changed</td>
</tr>
</tbody>
</table>
Vancomycin breakpoints for S. aureus

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

Vancomycin / Staphylococcus aureus
EUCAST MIC Distribution - Reference Database

MIC (mg/L)

% microorganisms

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

SR EUCAST
S R CLSI
Differences between EUCAST and CLSI vancomycin breakpoints for *S. aureus*

- No difference for susceptible isolates
- VISA reported resistant by EUCAST and intermediate by CLSI
- No difference for VanA-mediated vancomycin resistance
- hVISA no difference as not detected by either guidelines
EUCAST web-pages (www.EUCAST.org)

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, FESCI and ISC. The Steering Committee also consults experts within the fields of Infectious Diseases and Microbiology, pharmaceutical companies and susceptibility testing device manufacturers on EUCAST proposals.

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

http://www.EUCAST.org
### Enterobacteriaceae

#### Penicillins

<table>
<thead>
<tr>
<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>S ≤ R &gt;</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

1. For ampicillin breakpoints, the resistant breakpoint of >8 mg/L ensures that all isolates with resistance mechanisms are reported resistant. The wide range of dosages and intravenous versus oral administration significantly affect therapeutic efficacy. The unspecified susceptible breakpoint enables the user to categorize wild type *Escherichia coli* and *Proteus mirabilis* as either susceptible or intermediate to the aminopenicillins depending on dosing, route of administration and whether the infection is systemic or affects the urinary tract only.

#### Benzylpenicillin

<table>
<thead>
<tr>
<th>Ampicillin</th>
<th>Note¹</th>
<th>8</th>
<th>10</th>
<th>Note*</th>
<th>14</th>
</tr>
</thead>
</table>

A. Clinical MIC breakpoints allow laboratories to decide on the basis of national dosing practices whether *Enterobacteriaceae* without resistance mechanisms to ampicillin should be categorized as S or I. To categorize wild type *Enterobacteriaceae* as S use disk diffusion breakpoints of 14/14 mm; to categorize as I use 50/14 mm.

#### Ampicillin-sulbactam

<table>
<thead>
<tr>
<th>Note¹</th>
<th>8</th>
<th>10-10</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
</table>

2. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.

#### Amoxicillin

<table>
<thead>
<tr>
<th>Note¹</th>
<th>8</th>
<th></th>
<th>Note*</th>
<th></th>
</tr>
</thead>
</table>

3. For susceptibility testing purposes, the concentration of clavulanate is fixed at 2 mg/L.

#### Piperacillin

<table>
<thead>
<tr>
<th>8</th>
<th>16</th>
<th>30</th>
<th>18</th>
<th>15</th>
</tr>
</thead>
</table>

4. Ertapenem breakpoints relate to *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* only.

#### Cephalosporins

<table>
<thead>
<tr>
<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>S ≤ R &gt;</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

1. The cephalosporin breakpoints for *Enterobacteriaceae* will detect resistance mediated by most ESBLs and other clinically important beta-lactamas in *Enterobacteriaceae*. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. For epidemiological or infection control purposes laboratories may want to use a test which specifically screens for the presence of ESBLs.
Rationale Documents from EUCAST

The following Rationale Documents (see General Information on Rationale Documents) are currently available from EUCAST:

- [Amikacin v 1.2](#)
- [Ciprofloxacin v 1.9](#)
- [Colistin v 1.0](#)
- [Daptomycin v 1.0](#)
- [Doripenem v 1.0](#)
- [Doxycycline v 1.0](#)
- [Ertapenem v 1.3](#)
- [Fluconazole v 1.0](#)
- [Gentamicin v 1.2](#)
- [Imipenem v 1.3](#)
- [Levofloxacin v 1.5](#)
- [Linezolid v 1.0](#)
- [Meropenem v 1.5](#)
- [Metronidazole v 1.0](#)
- [Minocycline v 1.0](#)
- [Moxifloxacin v 2.3](#)
- [Mupirocin v 1.0](#)
- [Netilmicin v 1.1](#)
EUCAST Disk Diffusion Test Methodology

EUCAST has developed a disk diffusion test based on MH-media and calibrated to EUCAST clinical breakpoints. The zone diameter breakpoints are tentative during 2010 and several are in preparation. Regular updates will be published during 2010.

- 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)
- Zubereitung der Medien(2009)
- EUCAST Blättchendiffusionstest - Handbuch (v. 1.0 Dec 18, 2009)
- EUCAST Blättchendiffusionstest - Diashow (v. 1.1 Jun 3, 2010)
- EUCAST Blättchendiffusionstest - Ableshilfe (v 1.0, Jun 3, 2010)
- Preparación del medio para el estudio de sesibilidad con discos (v 1.1)
- Descripción del método de disco (v 1.1)
- EUCAST: método de difusión con discos para el estudio de la sensibilidad a los antimicrobianos (v 1.1, Jun 3, 2010)
# Breakpoint committees 2010

<table>
<thead>
<tr>
<th>Committee</th>
<th>Country</th>
<th>Disk diffusion test</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUCAST</td>
<td>Europe</td>
<td>Yes</td>
</tr>
<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>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>
</tr>
<tr>
<td>SRGA</td>
<td>Sweden</td>
<td>No</td>
</tr>
<tr>
<td>CLSI</td>
<td>USA</td>
<td>Yes</td>
</tr>
</tbody>
</table>
National Antimicrobial Susceptibility Testing Committees (NAC)

Remit:
To deal with questions related to antimicrobial susceptibility testing at a national level.

Membership:
Representatives of clinical microbiological diagnostic services
National experts on susceptibility testing of bacteria (and fungi)
Representatives of reference clinical microbiology laboratories
Government
Professional organisations/societies
Representatives of other antibiotic committees

Funding:
National level
National Antimicrobial Susceptibility Testing Committees objectives

- Strategy for antimicrobial susceptibility testing on national level
- Implementation of breakpoints and methods
- Quality assurance on a national level
- Education of laboratory staff and clinical colleagues
- Liaison and consultation with EUCAST (GC rep)
- Liaison with groups involved in resistance surveillance (ECDC EARS-Net, ....)
## EUCAST breakpoints and National Antimicrobial Susceptibility Testing Committees

<table>
<thead>
<tr>
<th>EUCAST/NABC:</th>
<th>NAC 2010/11:</th>
<th>Discussion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Austria</td>
<td>Croatia</td>
</tr>
<tr>
<td>Germany</td>
<td>Belgium</td>
<td>Greece</td>
</tr>
<tr>
<td>Norway</td>
<td>Denmark</td>
<td>Israel</td>
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<td>Sweden</td>
<td>Estonia</td>
<td>Poland</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Finland</td>
<td>Russia</td>
</tr>
<tr>
<td>The UK</td>
<td>Hungary</td>
<td>Turkey</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Lithuania</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>Latvia</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
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</table>
• Harmonised breakpoints for major antibacterial and antifungal agents
• Less common drugs and microorganisms identified and prioritized
• Breakpoints for new drugs as part of the approval process with EMA
• EUCAST breakpoints in European SPCs
• Review of several breakpoints

• ISO standardised MIC determination method
• EUCAST disk diffusion method
• Breakpoints implemented or in process in automated systems
• Website with all documents including breakpoint tables, QC tables, methodology and MIC and zone distributions

• Breakpoints implemented in countries with existing national breakpoint committees (France, Germany, Netherlands, Norway, Sweden, UK)
• Breakpoints being implemented in multiple other countries and NACs established