Antimicrobial susceptibility testing in human medicine in Europe – breakpoint committees

NCCLS is now CLSI

CLSI (USA)

BSAC wp  The UK
CA-SFM  France
CRG  Netherlands
DIN  Germany
NWGA  Norway
SRGA  Sweden

Eucast (EUROPE)
Many European countries subscribe to CLSI....
Breakpoints and methods used by lab:s in EARSS 2001

|      | UK | Sweden | Spain | Slovenia | Portugal | Poland | Netherlands | Malta | Luxembourg | Italy | Israel | Ireland | Iceland | Hungary | Greece | Germany | France | Denmark | Czech R. | Bulgaria | Belgium | Austria | Total |
|------|----|--------|-------|----------|----------|--------|-------------|-------|-------------|-------|--------|---------|---------|---------|--------|---------|--------|---------|----------|----------|---------|---------|
| BSAC | 12 |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 17     |
| CRG  | 6  |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 6      |
| Czech 98 |     |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 15     |
| DIN  |    |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 15     |
| FIRE |    |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 9      |
| Mensura |     |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 1      |
| CLSI | 25 | 7      | 11    | 18       | 8        | 1      | 5           | 50    | 3           | 1     | 3      | 1       | 14      | 6       | 12     | 4       | 20     | 31      | 9        | 229     |
| SFM  |    |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 1      |
| SRGA | 25 |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 26     |
| Stokes | 6  |        |       |          |          |        |             |       |             |       |        |         |         |         |        |         |        |         |          |          |         |         | 15     |
| >1 method | 3 | 5 | 3 | 1 | 1 | 9 | 2 | 2 | 9 | 4 | 1 | 11 | 10 | 61 |
| Not specified | 3 | 4 | 2 | 1 | 1 | 3 | 1 | 3 | 3 | 16 | 1 | 38 |

Last updated 20-02-2005
National breakpoint committees in Europe – what do they do?

- **breakpoint** committees
- guidelines on **methodology** (France, Sweden, the UK)
- internal and external **quality assurance**
- **education** of medical staff and laboratory personnel
- **surveillance** of antimicrobial resistance (national and international programs)
- **liaison** with regulatory authorities, the medical profession and pharmaceutical industry.

... maybe all countries should have one?!
EUCAST

European Committee on Antimicrobial Susceptibility Testing
formed in 1997 and restructured in 2002

convened by
European Society for Clinical Microbiology and Infectious Diseases
(ESCMID)
National Breakpoint Committees in Europe

and financed by
ESCMID
National Breakpoint Committees in Europe
DG-SANCO of the European Union (3 year grant from May 2004)
EUCAST

• a network of national breakpoint committees, experts and industry involved in antimicrobial susceptibility testing

• breakpoints for existing and new antimicrobial drugs

• epidemiological cut off values for surveillance of antimicrobial resistance

• promote standardisation and quality assessment of AST methods in Europe

• promote consensus on susceptibility testing

• collaborate with groups involved in antimicrobial susceptibility testing (CLSI) and the epidemiology of antimicrobial resistance (EARSS, ESGARS, ESAC).

• advise European Community Institutions

• devise and participate in programmes for education and training in antimicrobial susceptibility testing

Last updated 20-02-2005
EUCAST

General Committee
- One representative from each European country and ISC and FESCI
- Meets once a year in conjunction with the ECCMID meeting
- All tentative decisions referred to GC for comments

Steering Committee
- One representative from each national breakpoint committee in Europe
- Two representatives from the General Committee (2 years turnover)
- Meets 4 times a year

Industry email network
- All pharmaceutical and AST manufacturers are invited to comment on EUCAST tentative decisions.

Subcommittee on Antifungal Susceptibility Testing
- Standardised methods for susceptibility testing
- Define wild type MIC distributions
- Define breakpoints
EUCAST steering committee
Appointments 2005

- Gunnar Kahlmeter, chairman 2008
- Derek Brown, scientific secretary 2008
- BSAC (The UK) - Alasdair MacGowan 2008
- CA-SFM (France) - F Goldstein/C-J Soussy 2008
- CRG (The Netherlands) - Johan W. Mouton 2008
- DIN (Germany) - Arne Rodloff 2008
- NWGA (Norway) - Martin Steinbakk 2008
- SRGA (Sweden) - A Österlund/I Nilsson-Ehle 2008
- EUCAST rep 1 – Olga Stetsiouk (Russia) 2004 - 06
- EUCAST rep 2 – Francisco Soriano (Spain) 2004 - 06
EUCAST General Committee 2004-5

Austria Prof Helmut Mittermayer
Belgium Prof Jan Verhaegen
Bosnia Dr Selma Uzunovic-Kamberovic
Bulgaria Prof Krassimir Metodiev
Croatia Dr Arjana Tambic-Andrasevic
Czech Republic Dr Pavla Urbaskova
Denmark Dr Niels Frimodt-Møller
Estonia Dr Paul Naaber
Finland Dr Antti Nissinen
France Prof Claude-James Soussy
Germany Prof Bernd Wiedemann
Greece Prof Alkiviadis Vatopoulos
Hungary Dr Éva Bán
Iceland Dr Karl Gustaf Kristinsson
Ireland Dr Martin Cormican
Italy Prof Pietro Emanuele Varaldo
Lithuania Prof Arvydsas Ambrozaitis
Netherlands Prof John Degener
Norway Dr Martin Steinbakk
Poland Prof Waleria Hryniewicz
Portugal Prof Jose Melo Cristino
Romania no representative
Russia Dr Olga Stetsiouk
Serbia Dr Lazar Ranin
Slovak Republic Prof. Milan Niks
Slovenia Dr Jana Kolman
Spain Dr Francisco Soriano
Sweden Dr Barbro Olsson-Liljequist
Switzerland Prof Jaques Bille
Turkey Dr Deniz Gür
UK Prof Alasdair MacGowan
Yugoslavia no representative

ISC – Paul Tulkens
FESCI – David Livermore

Network of industry with an interest in antimicrobials

Chairman Gunnar Kahlmeter, Sweden
Scientific secretary Derek Brown, UK

Last updated 20-02-2005
Authority of breakpoint committees?

- Breakpoint committees have **no legal authority** – only a "scientific mandate". This is shared by EUCAST, CLSI, BSAC, CA-SFM, CRG, DIN, NWGA, SRGA.

  The authority rests with National medicine’s agencies, EMEA and FDA.

- However, a working relationship between EMEA and EUCAST is being developing.
The SOP allows EUCAST to interact with the EMEA rapporteur and expert and the pharmaceutical company at the earliest stage of the registration process and to suggest to EMEA breakpoints for the new drug to be formally included in the SPC (summary of product characteristics) of the drug.

The purpose is to avoid discrepancies between ”regulatory” breakpoints and those of the profession.

Until now EMEA SPCs (”summary of product characteristics”) have contained breakpoints from ”all” the national European breakpoint committees and NCCLS.

In 2004 the CHMP decided that future SPCs will contain EUCAST breakpoints instead of other breakpoints
The SOP can be downloaded from the EUCAST homepage (www.eucast.org) and from the EMEA homepage.
Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

- Cephalosporin breakpoints for Enterobacteriaceae
- Carbapenems and Monobactams (!?)

CEN and ISO (EUCAST and CLSI) – international reference method for determination of MICs for non-fastidious bacteria.
Collaboration

**EUCAST AFST** – will use EUCAST terminology, wild MIC distribution concept, procedure for breakpoint setting and connections with EMEA.

**Expert groups** on Neisseria gonorrhoeae, Neisseria meningitidis, Anaerobes, VetCAST and others have accepted our invitation to join The consultation process.
All official EUCAST documents, tables, recommendations, meetings, minutes etc go on the freely available website www.eucast.org.

Since being re-structured in 2002, EUCAST has:

- Agreed on a principal model for harmonising breakpoints for new antibiotics in Europe. EMEA and EUCAST are now discussing a suitable protocol by which EUCAST breakpoints may become part of the official registration process of new antimicrobials.
- Agreed on a principal model for harmonising breakpoints for existing antibiotics in Europe. The aminoglycosides, fluoroquinolones, glycopeptides and oxazolidinones have now received tentative European breakpoints (available for comments on the EUCAST website) and the process now continues with carbapenems and cephalosporins which should be completed during 2004.
- Devised web-based software for the collection and presentation of wild-type MIC distributions of relevant drug/bug combinations. The program is available through a link from the EUCAST website.
Antimicrobial wild type distributions of microorganisms

The EUCAST (European Committee on Antimicrobial Susceptibility Testing) under the auspices of the ESCMID (European Society for Clinical Microbiology and Infectious Diseases) offers this free website of distributions of MIC-values of wild type bacteria and fungi.

Each MIC-distribution is defined by the micro-organism, the antimicrobial drug and the method. It is the compound result of a number of separate distributions submitted to EUCAST from organizations such as national breakpoint committees, industry, antimicrobial resistance surveillance programs and research projects. Each distribution has been released by the EUCAST steering committee and thereby also by the national breakpoint committees which help form the EUCAST steering committee. The distributions are used by the committee for defining epidemiological cut-off values to for surveillance of resistance development, and for the harmonisation of European clinical breakpoints.

Each graph contains information on the number of sources of data, the total number of organisms, and when defined by EUCAST, clinical breakpoints (≤ 2 mg/L and > 2 mg/L) and/or the epidemiological cut-off value. The epidemiological cut-off value is related to the MIC distribution of the wild type organism and categorized as WT≥2 mg/L.

Questions can be addressed to gunnar.kahler@tkrknorborg.se

www.eucast.org
Antimicrobial wild type distributions of microorganisms

Search

Method: círculo MIC • círculo Disc diffusion
Antimicrobial: Vancomycin • deslizante Species: Species...

Antimicrobial: Vancomycin (Method: MIC)

|                         | 0.002 | 0.004 | 0.008 | 0.016 | 0.032 | 0.064 | 0.125 | 0.25 | 0.5  | 1    | 2    | 4    | 8    | 16   | 32   | 64   | 128  | 256  | 512  |
|-------------------------|--------|--------|--------|--------|--------|--------|--------|------|------|------|------|------|------|------|------|------|------|------|
| Enterococcus faecalis   | 0      | 0      | 0      | 0      | 0      | 2      | 15     | 250  | 1552 | 1590 | 214  | 8    | 3    | 1    | 17   | 15   | 4    |
| Enterococcus faecium    | 0      | 0      | 0      | 0      | 0      | 1      | 35     | 676  | 1275 | 158  | 39   | 16   | 2    | 3    | 5    | 1    | 52   | 3    |
| Propionibacterium acnei| 0      | 0      | 0      | 0      | 0      | 0      | 13     | 150  | 131  | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Staphylococcus aureus   | 0      | 0      | 0      | 0      | 0      | 52     | 440    | 818  | 35433| 3215 | 57   | 3    | 0    | 1    | 1    | 0    | 0    | 0    |
| Staphylococcus capitis  | 0      | 0      | 0      | 0      | 0      | 5      | 28     | 110  | 25   | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Staphylococcus coagulase negative | 0 | 0 | 0 | 0 | 0 | 52 | 352 | 2978 | 3554 | 155 | 6 | 2 | 0 | 0 | 0 | 0 |
| Staphylococcus cohnii   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 18   | 2    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Staphylococcus epidermidis | 0 | 0 | 0 | 0 | 0 | 2 | 21 | 180 | 2699 | 3914 | 145 | 2 | 0 | 0 | 0 | 0 | 0 |
| Staphylococcus haemolyticus | 0 | 0 | 0 | 0 | 0 | 7 | 72 | 503 | 332 | 34 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Staphylococcus hominis  | 0      | 0      | 0      | 0      | 0      | 0      | 6      | 52   | 256  | 88   | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Staphylococcus intermedius | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 10 | 13 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Staphylococcus lugdunensis | 0 | 0 | 0 | 0 | 0 | 2 | 16 | 44 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Staphylococcus saprophyticus | 0 | 0 | 0 | 0 | 0 | 0 | 14 | 138 | 59 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Staphylococcus simulans | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 9    | 53   | 24   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Staphylococcus warneri  | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 10   | 71   | 35   | 2    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Streptococcus agalactiae| 0      | 0      | 0      | 0      | 0      | 0      | 0      | 106  | 176  | 5    | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Streptococcus anginosus | 0      | 0      | 0      | 0      | 0      | 2      | 3      | 42   | 39   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Streptococcus bovis      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 54   | 144  | 12   | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
Vancomycin / Staphylococcus aureus

Antimicrobial wild type distributions of microorganisms – reference database EUCAS

MIC
Epidemiological cut-off: WT ≤ 4 mg/L

70630 observations (22 data sources)
Clinical breakpoints: S ≤ 4 mg/L, R > 8 mg/L
"Wild type" MIC distributions

1. reference for **calibration of antimicrobial susceptibility testing methods**

2. to define **epidemiological cut-off values**

3. reference material for committees involved in decisions on **clinical breakpoints**

4. reference **MIC ranges** for a wide spectrum of species and antimicrobials

5. an opportunity to **measure and compare resistance** development in bacteria that lack breakpoints or are classified as naturally resistant (Enterococci vs. Gentamicin)
EUCAST procedure for setting breakpoints
1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

### National breakpoint committees

<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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common dose</strong></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>2-400 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><strong>Maximum dose schedule</strong></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>data pending</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><strong>Available formulations</strong></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>
</tbody>
</table>

### Clinical data

There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* with low-level Fluoroquinolone resistance (MIC > 0.064 mg/L) EUCAST has suggested that the epidemiological cut off value (S<0.064/R>0.064 mg/L) be used in Salmonella systemic infections. These strains are best found using a nalidixic acid 30 µg screen disc in routine susceptibility testing.

There is agreement in EUCAST that ciprofloxacin activity against Enterococci and Streptococci, including S.pneumoniae, is insufficient to categorize wild type bacteria “susceptible”.

Last updated 20-02-2005
2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT \leq X \text{ mg/L})
### 3. Existing national clinical breakpoints are compared

*Ciprofloxacin* was used in this example:

<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>NCCLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General breakpoints</strong></td>
<td>ND</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>0.125/2</td>
<td>1/2</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>0.12/2</td>
<td>0.12/1</td>
<td>1/2</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>1/4</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>1/1</td>
<td>1/2</td>
</tr>
<tr>
<td><em>Acinetobacter</em> 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><em>Streptococci</em></td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/2</td>
<td>excl</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>2/2 (I)*</td>
<td>excluded</td>
<td></td>
<td></td>
<td>0.12/2 (I)*</td>
<td>0.12/2 (I)*</td>
<td>excl</td>
</tr>
<tr>
<td><em>Enterococci</em></td>
<td>excluded</td>
<td>excluded</td>
<td></td>
<td></td>
<td>0.12/2</td>
<td>0.12/2</td>
<td>1/2</td>
</tr>
<tr>
<td><em>Haemophilus/Moraxella</em> 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><em>Corynebacteria</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>excl</td>
<td></td>
</tr>
<tr>
<td><em>N. Meningitidis</em></td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td>0.06/0.12</td>
<td>0.03/0.25</td>
<td></td>
</tr>
<tr>
<td><em>N. Gonorrhoeae</em></td>
<td>0.06/-</td>
<td>0.06/1</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><em>P. Multocida</em></td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>0.12/0.25</td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>excluded</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>excluded</td>
<td></td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>2/2</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

Last updated 20-02-2005
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 resulting in optimal outcome is determined from:

- in vitro data
- animal studies
- clinical trials

In each of the model systems, as well as results from clinical trials, Pk/Pd analyses are performed on outcome data if possible. The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated
6. Using available Pk/Pd data, Monte Carlo simulations are performed and a Pk/Pd breakpoint is calculated. It is based on conventional dosing regimens.

\[ S = 0.5 \text{ mg/L} \quad \text{Pk/Pd} \quad S = 1 \text{ mg/L} \]
7. Clinical data relating outcome to MIC-values, wild type and resistance mechanisms are assessed in relation to the tentative breakpoint

"Minimum requirement for S-category" is that the upper value of the wild type MIC-distribution is < the MIC derived from the Pk/Pd index needed for optimal efficacy based on free drug". 
8a. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example ciprofloxacin.

...it was decided to set the break-point at \( S \leq 0.125 \) and \( R > 2 \) mg/L, rendering wild type \( S. pneumoniae \) immediately susceptible to ciprofloxacin.

Epidemiological cut off: WT\( \leq 2.0 \)

Splitting the wild type must be avoided to permit reproducible susceptibility testing!
8b. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin

... a break-point of 2 mg/L was acceptable with a footnote that this relates to high dose therapy.

Epidemiological cut off: WT<2.0

Splitting the wild type must be avoided to permit reproducible susceptibility testing!
9. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for (written) comments. When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

10. Consultation process on tentative breakpoints:
   - EUCAST general committee
   - Expert committees (Neisseria, Anaerobes, others)
   - Pharmaceutical industry, AST device manufacturers
   - Others via EUCAST website

11. Rationale document prepared and published on website
### Fluoroquinolones - EUCAST clinical MIC breakpoints

#### Species-related breakpoints (S<\(\leq\)R>)

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Entero- bacteriaceae</th>
<th>Streptococcus A,C,G</th>
<th>S.pneumoniae</th>
<th>H.influenzae</th>
<th>M.catarrhalis</th>
<th>N.gonorrhoeae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>--</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5</td>
<td>0.03/0.06</td>
<td>--</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1/2</td>
<td>1/2</td>
<td>2/2</td>
<td>1/1</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>IE</td>
<td>IE</td>
<td>0.5/1</td>
<td>1/2</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5</td>
<td>0.12/0.25</td>
<td>--</td>
</tr>
</tbody>
</table>

#### Non-species related breakpoints

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Entero- bacteriaceae</th>
<th>Streptococcus A,C,G</th>
<th>S.pneumoniae</th>
<th>H.influenzae</th>
<th>M.catarrhalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>--</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5</td>
<td>--</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1/2</td>
<td>1/2</td>
<td>2/2</td>
<td>1/1</td>
<td>--</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>IE</td>
<td>IE</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>IE</td>
<td>--</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5/1</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5</td>
<td>0.5/1</td>
</tr>
</tbody>
</table>

---

1. For breakpoints for other fluoroquinolones (e.g. pefloxacin and enoxacin) refer to breakpoints determined by national breakpoint committees.
2. Salmonella spp - there is clinical evidence for ciprofloxacin in infections caused by Salmonella spp, with low-level resistance (MIC<0.064 mg/l) found in case reports of poor response with other fluoroquinolones. Since no such clinical evidence exists for other fluoroquinolones, breakpoints determined for ciprofloxacin are therefore categorized as intermediate. For all other fluoroquinolones breakpoints for ciprofloxacin and other fluoroquinolones are the same. Therefore, breakpoints for ciprofloxacin may be used as a reference to set breakpoints for other fluoroquinolones.
3. *Streptococcus pneumoniae* - the breakpoints for ciprofloxacin against *S.pneumoniae* were increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution.
4. *Haemophilus/Moraxella* - fluoroquinolone MIC breakpoints are the same as from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin and are therefore categorized as intermediate. For levofloxacin and other fluoroquinolones breakpoints for levofloxacin may be used as a reference to set breakpoints for other fluoroquinolones.
5. *Neisseria meningitidis* - breakpoints for ciprofloxacin are not yet defined since only few clinically resistant strains have been reported.
6. *Neisseria meningitidis* - breakpoints for ciprofloxacin are not yet defined since only few clinically resistant strains have been reported.
7. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.
### Carbapenems - EUCAST clinical MIC breakpoints 23 November 2004

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Streptococcus</th>
<th>Enterococcus</th>
<th>Staphylococcus Aureus</th>
<th>M. catarrhalis</th>
<th>N. meningitidis</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints (S&lt;R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cephalosporins - EUCAST clinical MIC breakpoints 18 February 2005

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Streptococcus</th>
<th>Enterococcus</th>
<th>Staphylococcus Aureus</th>
<th>M. catarrhalis</th>
<th>N. meningitidis</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints (S&lt;R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Aztreonam - EUCAST clinical MIC breakpoints 23 November 2004

<table>
<thead>
<tr>
<th>Aztreonam</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Streptococcus</th>
<th>Enterococcus</th>
<th>Staphylococcus Aureus</th>
<th>M. catarrhalis</th>
<th>N. meningitidis</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints (S&lt;R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ongoing breakpoint harmonisation**

1. Enterobacteriaceae - the S/R breakpoint was decreased to 4 μg/mL so as not to miss ESSRLs.
2. Pseudomonas
3. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with - or IE in the table).

**Status:**
- Preliminary breakpoints: 2004-11-23
- Open for consultation with national breakpoint committees.
- Breakpoints to be finalised: March 2005.

**Breakpoints finalised at EUCAST Steering committee meeting: YEAR-MONTH-DAY.**

EUCAST 2004 (The European Committee on Antimicrobial Susceptibility Testing)

Updated 2004-11-23, O Halimater
How to implement EUCAST breakpoints

- The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using one of the European national systems will gradually adhere to the European breakpoints.

- Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions (local and national surveillance, EARSS, etc).

- Systems for automated susceptibility testing can be set up with EUCAST MIC breakpoints.

- Through an agreement between EMEA, EFPIA and EUCAST new antimicrobials will be given breakpoints through EUCAST as part of the registration process. The SPC for these drugs will contain only EUCAST breakpoints.
EUCAST future activity

- Cephalosporin, carbapenem and aztreonam breakpoints to be completed during 2005
- Commence work 2005 on harmonising penicillin breakpoints
- EMEA SOP for registration of new drugs implemented for 2 new antibacterial drugs
- Rationale documents for breakpoints extended and made available on the website (links from the breakpoint tables)
- Documents for update
- EUCAST/EARSS Workshop in Rome - 23-25th of November, 2005
EUCAST

Thank you