Consultation on breakpoint changes necessary in conjunction with introducing new definitions of S, I and R in the EUCAST breakpoint Table v 9.0.

Consultation 4 October – 4 November, 2018

Background.
EUCAST has decided to change the definitions of susceptibility testing categories S, I and R as shown below. The result of several consultations is available on the EUCAST website under “Consultations”.

| S - Susceptible, standard dosing regimen: A microorganism is categorised as Susceptible, standard dosing regimen, when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent. |
| I – Susceptible, increased exposure: A microorganism is categorised as Susceptible, Increased exposure* when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection. |
| R - Resistant: A microorganism is categorised as Resistant when there is a high likelihood of therapeutic failure even when there is increased exposure. |

*Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

Terminology
- Susceptibility testing categories: S, I and R.
- Report isolates S, I or R.
- Describe isolates as belonging to the S, I or R categories.
- Describe isolates as susceptible (S and I) or resistant (R).
- When an isolate is described as susceptible, this excludes resistant.
- When an isolate is described as resistant, this excludes susceptible (S and I-categories).
- For surveillance purposes, avoid lumping categories – record as S, I and R. If lumping does occur, never lump I and R, only S and I.
The new definitions are clearly related to agent exposure of the organism which is in turn related to dose, dosing frequency (including going from repeated administration to intravenous infusion), dosing route and to the pharmacokinetics of the agent and sometimes to the type of infection (urinary tract infections vs. meningitis). An I-category assumes that it is possible to increase the exposure by one of the means listed above. Nevertheless, in the current EUCAST breakpoint tables, there are a few breakpoints where this logic does not hold and, in conjunction with the change in definitions, we propose to correct this.

For Enterobacterales, some agents are only indicated for urinary tract infections and the S- and R-breakpoints without an I-category were determined to reflect this use of the agent. A change is not needed. This is the case for the following agents: cefadroxil, cefalexin, cefixime, cefpodoxime, cefitube, cefuroxime oral, norfloxacin, trimethoprim, mecillinam, nitrofurantoin, nitroxoline. A change is not needed.

A few agents have already been assigned separate breakpoints for, on one hand, systemic therapy and, on the other, the treatment of uncomplicated UTI caused by Enterobacterales. These are amoxicillin/clavulanic acid and fosfomycin. A change is not needed.

For a few agents the current breakpoints need to be modified to better fit the new definition of the "I-category" or because there is a historical inconsistency between different members within the agent group.

The table below excludes necessary changes in the aminoglycoside group and for tigecycline since for other reasons these are subject to reviews and separate consultations:

<table>
<thead>
<tr>
<th>Species group</th>
<th>Agent</th>
<th>Current breakpoint (mg/L)</th>
<th>Proposed breakpoint (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <em>Pseudomonas</em></td>
<td>Aztreonam</td>
<td>1 / 16</td>
<td>16 / 16</td>
</tr>
<tr>
<td>2. <em>Enterococcus</em></td>
<td>Trimethoprim</td>
<td>WT I-category</td>
<td>Note + ECOFF</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em></td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>WT I-category</td>
</tr>
<tr>
<td>3. <em>N. meningitidis</em></td>
<td>Chloramphenicol</td>
<td>2 / 4</td>
<td>2 / 2</td>
</tr>
<tr>
<td>4. <em>H. influenzae</em></td>
<td>Cefpodoxime</td>
<td>0.25 / 0.5</td>
<td>0.25 / 0.25</td>
</tr>
<tr>
<td>5. <em>Proteus, Morgaenella, Providencia</em></td>
<td>Imipenem</td>
<td>2 / 4</td>
<td>0.12 / 4</td>
</tr>
<tr>
<td>6. <em>Acinetobacter</em></td>
<td>Ciprofloxacin</td>
<td>1 / 1</td>
<td>0.06 / 1</td>
</tr>
</tbody>
</table>

1. For *Pseudomonas*, agents should be administered to achieve the highest possible exposure. This is true for almost all anti-pseudomonas agents. The option to place wild type *Pseudomonas* isolates in the I-category (which would be the logical decision to take) was discussed, but it is feared that the adverse consequences of having only carbapenems in the S-category would be worse. Therefore, classical agents for treating wild-type *Pseudomonas aeruginosa* will, for at least one more year, continue to be included in the S-category but with a
note to emphasise the need for the highest exposure. For aztreonam organisms have MICs of 1 – 16 mg/L, with 90 - 95 % at 2 – 8 mg/L. The ECOFF is 16 mg/L. High dose aztreonam (2 g x4 iv) allows for a breakpoint of 16 mg/L. In the version 9.0 of the breakpoint table wild type *Pseudomonas*, will be categorised susceptible but with a comment to say that the highest possible exposure should be assured.

2. **Enterococcus** vs. trimethoprim and trimethoprim-sulfamethoxazole. Following extensive discussions about the activity of trimethoprim against enterococci in urine, wild type organisms of *E. faecalis* and *E. faecium* were placed in the I-category to emphasize the uncertainty. With the current changes, we propose that breakpoints are changed to a **Note** referring to the uncertain activity of the agents in urine and that the ECOFF is added to the Note.

3. **N. meningitidis** and chloramphenicol. This breakpoint was introduced over 15 years ago as part of an attempt to harmonise with other committees. There is no scientific basis for recommending an I-category for chloramphenicol and a **Note** is added stating that “The breakpoint applies to high dose therapy in meningitis and septicaemia”.

4. **H. influenzae** vs. cefpodoxime. There is no high dose for cefpodoxime and hence not logical to have an I-category.

5. **Proteus, Morganella and Providencia** vs. imipenem – the intrinsic activity of imipenem is lower for these species than for other Enterobacterales and it is proposed that the breakpoints place wild type organisms of these species in the I-category to emphasize the need for the highest exposure.

6. **Acinetobacter spp.** vs. ciprofloxacin – to emphasize the need for the highest possible exposure in the treatment of *Acinetobacter* infections, EUCAST aims to place wild type *Acinetobacter* spp in the I-category.

There are now a few situations in the table where the entire wild type population of a species is categorised “Susceptible, increased exposure”. These will remain:
- **Cefuroxime-axetil** (cefuroxime oral) vs. *Haemophilus influenzae* and *Moraxella catarrhalis*.
- **Cefaclor** and *Streptococcus pneumoniae*.
- **Imipenem** vs. **Proteus, Morganella and Providencia**.
- **Ciprofloxacin** vs. *Acinetobacter* spp.

It is the intention of EUCAST to **discuss** and **consult** during 2019 on the following related issues in preparation for the breakpoint table v10.0 (2020):
- To place wild type *Pseudomonas aeruginosa* in the I-category to emphasise the need for high exposure for most anti-pseudomonal agents.
- To place wild type Enterobacterales in the I-category (instead of the S-category) for aminopenicillins and cefuroxime, again to emphasise the need for high exposure even in isolates devoid of resistance mechanisms.

These changes will, following consultation and agreement, be implemented in EUCAST breakpoint table v9.0 (1 January, 2019).