**Comments and Responses for Consultation on: Aminoglycosides Breakpoints**  
**Date: 2 March, 2020**

<table>
<thead>
<tr>
<th>Comment from (name, contact details)</th>
<th>Comments</th>
<th>EUCAST Responses</th>
</tr>
</thead>
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| NWGA, Christoffer Lindemann        | NWGA support the proposed revision of aminoglycosides breakpoints. The continued use of aminoglycosides as practiced in Norway is dependent on the note replacing systemic breakpoints being presented in its current form. NWGA does not see a need for a gentamicin UTI-bp for *Pseudomonas* spp, but will not oppose an inclusion in the table | **Response:** Thank you for your comments. A UTI breakpoint for gentamicin and *Pseudomonas* spp. is not proposed.  
**Action:** None required |
| **First email**                     | Congratulations for the EUCAST team for the great work you have been doing and the great contribution to make antibiotic prescription more intelligent and safe. This aminoglycosides BP revision is really great.  
I am MD and I work with antibiotic stewardship in Brasil. I have been using PK/PD breakpoints to choose the right antibiotic and the right dosing for many years. With the increased GNB MDR many doctors are using aminoglycosides empirically or not, and unfortunately with the wrong dosing and the overestimated BPs are making it much worse.  
There is a vice of cognition that aminoglycosides is always working as a second drug, and that any dosing could be used. I guess that for empirical use it is a great mistake, as many GNBs MDR are only susceptible to amikacin, for example, and the sub-optimal dosing since the beginning of therapy will carry the risk of | **First email**  
**Responses:** Thank you for your feedback. A number of your comments and suggestions relate to possible changes to the consultation document itself. A number of comments from others have raised the issue of the amikacin doses. The current evidence available to EUCAST shows that doses lower than 30mg/kg/day, while reducing the risk of toxicity, would result in breakpoints within wild type distributions and consequent poor test performance.  
**Actions:** None required |
toxicity without the antibacterial benefit, so this should be seriously avoided.
I have to explain and give talks to the MDs why that is happening very frequently, and not only with AMG and other antibiotics with overestimated BP.

The graphics with the MCS, different TARs and MICs distribution are excellent and smart.

Table 21 is very clear and didactic.

Maybe there should be included in the table the dosing MIC guided, for example, smaller dosing (20mg/kg) for Amikacin MIC of 1mcg/mL?, to decrease the risk of toxicity?

In Brasil it is different from Europe and Australia, it not usual to have MD doctor in the micro Labs in the hospitals, so interfacing LAB AST and the MD is frequently a problem in many hospitals.

Because many MD do not understand PK/PD and the AST, so the inclusion of dosing as EUCAST have already been doing is extremely helpful.
It is a life time job to teach MD how to use antibiotics properly.

Second email
I would like to complement my previous comments about the aminoglycosides breakpoints:

1- It would be interesting to add the references of PD data from table 19.

2- For me, it was not very clear the calculation of AUC ELF Lung target index.

Second email
Responses:
Detailed references are normally included once decisions are final and rationale documents are updated.
EUCAST does not usually provide commentary on other proposed breakpoints or those set by other organisations.
EUCAST already supports once-daily dosing, as shown in the Dosages tab of the
3- The proposed breakpoints for monotherapy are lower than from some of the previous studies (for example, G. L. Drusano and Arnold Louie Optimization of Aminoglycoside Therapy ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2011, p. 2528–2531); probably because the BPs of the previous studies were based on clinical response, and the EUCAST proposed new BPs are based on PK/PD/animal model/bacterial load log reduction.

4- Wouldn’t it be interesting to explain the differences of these breakpoints? As the clinical use of aminoglycosides will be markedly reduced with the new breakpoints.

5- I guess that it would be interesting to add the references or methods of the calculations of the MCS showed in the graphics.

6- It would be important to point it out that toxicity is decreased with the extended once a day dosing, as in the graphics the AUC:MIC and TARs/PTA look similar with both traditional and extended dosing.

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<td>1-On Table 19, there are no references for the PD targets for lung and thigh data. Would the data have come from the study from Dr Craig? I guess that the reference should be included. J Antimicrob Chemother. 1991 May;27 Suppl C:29-40. Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. Craig WA1, Redington J, Ebert SC</td>
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<td>2- For me, it is not clear yet why AUCs are higher in thigh model of infection than in the lungs model of infection. The differences in AUC/MIC targets in lung and thigh wouldn’t be related to local aminoglycosides concentration? Aminoglycosides are hydrophilic Breakpoint Tables, and thus indirectly promotes the reduced (nephro)toxicity with this mode of administration.</td>
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**Actions:** Relevant references will be added when the rationale documents are updated. Importantly, the consultation document is not a “permanent” document, but meant only to support decision-making.

**Responses:** As noted above, relevant references will be added to the rationale documents once decisions on breakpoints are finalised.

The differences in targets for thigh versus lung models come from animal model experiments, and not from lung ELF pharmacology alone. We agree that the proposed revision will be considered radical by many. There is a fine balance here between ensuring efficacy
antibiotics and the concentrations in the alveoli are expected to be lower than the serum. In table 19, there is an information, that the concentration rate ELF/serum was considered to be 1. In Craig study, it was mentioned that aminoglycosides muscle concentrations were close to serum concentration. In table 19, the AUCs for lungs are lower than for thigh. Craig in the study mentioned above, had the hypothesis that it could be related to PAE in the lungs, and/or prolonged concentration in the lungs. That is the explanation?

3-The MCS graphics are clear and smart, however, there are no references or explanation how they were done.

4-These new breakpoints changes are radical and MD will call the lab to complain about the lack of options to treat CRE, for instances. I understand that it is not EUCAST fault as you are making aminoglycosides prescription much safer.

5-I understand that dosing was not studied by EUCAST, nonetheless, you might consider to mention breakpoints for PK/PD 1 log reduction/killing and for stasis including the explanation that a second active drug should be associated to treat a systemic infection.

6-MDs usually prescribe aminoglycosides with wrong dosing, especially in countries where there are high rate of GNB MDR and no pharmacists or antibiotic stewardship specialists. In Brazil, EUCAST will substitute CLSI probably this year or next year and it would be a great opportunity to suggest dosing and different breakpoints for PK/PD and stasis for the therapy of GNB MDR systemic infections.

4th and 5th emails
On the table below the proposed PK-PD breakpoint for Amikacin and minimising toxicity of these agents.

Breakpoints for a 1-log kill will not be possible because these would be within the wild-type distribution resulting in a poorly-performing test. We have included a statement about avoiding their use as monotherapy in systemic infections outside the urinary tract, which implies the use of a second agent.

**Actions:** EUCAST will add a statement about using adjunct active therapy for systemic infections outside the urinary tract.
for 1 kill for systemic infections shows that it is 1mcg/mL, wouldn’t it be 2mg/L?
The Stasis breakpoint for Amikacin is 4mg/L.

As we can see in the Monte Carlo Simulation Graphics and table below, they show that the probability of Target Attainment for 1 log₁₀ kill for MIC of 2mg/L is 92% for amikacin 20mg/kg and 99% for amikacin 30mg/day in the thigh infection animal model. On table 21 the amikacin PK-PD BP is 2mcg/mL

What would be the final proposed amikacin BP for systemic infections?

4th and 5th emails
Responses:
The target attainment rate for a 1-log kill with amikacin in the thigh model at 2mg/L is less that 95%, which is the usual minimum rate aimed for by EUCAST. Thank you for noticing the error in Table 21.

Actions: Table 21 will be amended in the final version of the rationale document, if it is included therein.

Søren email about German NAC (not a formal submission)
Most people are also ok with the Aminoglycosides document but want guidance on the use of these drugs in combinations. I told them there will probably be one that says “if the MIC is below the ECOFF then the isolate is (most probably) wild type” (which they could have guessed themselves), this does, however, say nothing about the usefulness of a combination nor about the dose needed. I asked them to come up with any data and testing procedure that would predict clinical utility of a combination (besides the one we already know in enterococci).

Responses:
We agree that there is concern about the lack of information about the use of these agents in combination.

Actions: The published evidence for which agents are relevant needs to be examined – however, there are national traditions, experience and guidelines that need to be respected.

Dr. Elske Sieswerda, clinical microbiologist and epidemiologist and Dr. Karin van Dijk, clinical microbiologist and epidemiologist, head of Department of Bacteriology, TBC and Mycology
Page 3: General We thank the EUCAST for the work.

Page 3: After reading the document and the Monte Carlo simulations, we don’t understand why there is a different approach for the aminoglycosides in Pseudomonas spp (i.e. a note for amikacin and tobramycin in systemic infections and a “-” for gentamicin, indicating it should not be used). In the simulation tables none of the aminoglycosides has acceptable target attainment and it seems that gentamicin and amikacin have similar

Responses:
For Pseudomonas spp., the majority of wild-type strains are covered by high dose regimens of amikacin and tobramycin, but significantly fewer by gentamicin, for which MIC-values are often 2 dilutions lower than for tobramycin.
| Page 3: | Similarly, we don’t understand the choice of 5 mg/kg for S. aureus as the presented Monte Carlo simulation used 7 mg/kg according to the table at page 24.
| Page 9: | We believe that the choice of breakpoints for UTI only are not explained very well, could EUCAST please elaborate on the choice of breakpoints for UTI? Also, to us it was not very clear if this includes complicated UTI. It seems EUCAST includes complicated UTI for the UTI breakpoints based on the comment at page 27. However, complicated UTI could also be seen as a systemic infection, so it would be nice if EUCAST could explain if complicated UTI should be seen as systemic or UTI only.
| Page 18: | It would be nice if the table columns would be aligned.
| Page 19: | At 4.2.2. you discuss the pharmacodynamics target values. When discussing PK/PD of aminoglycosides, many physicians state that “aminoglycosides sterilize the blood rapidly” and are therefore interpreted as very effective for bacteraemia. Currently, the EUCAST table at this page states that mouse thigh and lung models were used for target value determination and that it was assumed that the murine ELF (epithelial lining fluid?) AUC value to total-drug plasma AUC value approaches 1. It would be very helpful to provide references for this assumption, as we learned this 1:1 ratio is not the case in humans (Kucers, 6th edition 2010, page 681). Also, it would be very helpful to provide a similar statement about the thigh to total drug plasma AUC, including references.
| Page 26: | We would like to ask the committee if the MIC for ≥95% in bacteriostasis for S. aureus in the thigh model is truly 0.5 or if it should be 1 mg/L based on the table at page 24 (stating that with

| Actions: | EUCAST will review the apparent
extended interval there is 97.1% target attainment of gentamicin 7 mg/kg for net bacterial stasis at MIC 1 mg/L of *S. aureus*.

**Page 27:** We suggest that data from the Cochrane systematic review of Paul et al 2014 (DOI: 10.1002/14651858) summarizes useful clinical data on efficacy and adverse events of combination therapy with aminoglycosides and beta-lactams. Especially the subgroup of 43 studies comparing beta-lactam + aminoglycoside with a broader spectrum beta-lactam suggests that a broader spectrum beta-lactam might be more effective and less toxic.

Also the studies of Allou 2016 (doi: 10.1007/s10096-016-2652-6 and 10.1186/s13613-016-0211-z) and Hodiamont 2017 (doi: 10.1097/FTD.0000000000000432) might be worth mentioning. These PK/PD studies confirmed that subtherapeutic drug levels and overexposure to aminoglycosides are common in seriously ill patients.

**NZ NAC (Sarah Underwood – NZNAC coordinator- sarah.underwood@esr.cri.nz)**

Aminoglycosides should be avoided as monotherapy in therapy of systemic infections caused by *Enterobacterales* (page 9, note 2).

The statement suggesting that monotherapy outside UTI using aminoglycosides should be avoided is too simplistic.

Choosing to structure a regimen that is not based on aminoglycosides would be due to considerations around toxicity or around aminoglycoside pharmacokinetics in some situations but aminoglycosides still have a role to play in bacteraemic/systemic UTI.

A suggested less definitive statement is “Aminoglycosides should be used with caution as monotherapy in systemic infections caused by *Enterobacterales*”. This would allow the use of a single dose of aminoglycoside to treat a UTI with a secondary bacteraemia, which would be classified as a “systemic infection”.

**Responses:**
Thank you for your thoughts about this statement. We have not been clear that the UTI breakpoints apply to bacteraemic UTI, based on the meta-analysis of Vidal et al. The evidence for efficacy as monotherapy in other systemic infections was weak according to that meta-analysis. We agree that there are important stewardship considerations, including the use of aminoglycosides as ‘carbapenem-sparing’ agents.

From other feedback, a variety of amikacin doses are used routinely around the world. However, our advice and breakpoints is based on the 20 and 30 mg/kg/day, and that EUCAST is concerned that 15 discrepancy in the breakpoint proposal for *S. aureus* and gentamicin versus dosing regimen.

EUCAST will review the papers on UTI in the Vidal meta-analysis to determine whether the UTI breakpoints should apply to complicated UTI.

EUCAST will review the additional quoted references (Paul et al., 2014; Allou 2016 and Hodiamont 2017).
under the proposed changes. Maintaining the possibility of aminoglycoside monotherapy assists in avoiding the use of carbapenems, from a stewardship point of view. Would prefer to keep a single breakpoint; ie not distinguishing between systemic infections and UTI. Amikacin dosing recommendations (p.8): 15mg/kg has been used in NZ.

**Actions:**
EUCAST will develop some clearer advice about what conditions the UTI breakpoint applies to.

| Dr Norelle Sherry (member of AusNAC) |
| norelle.sherry@austin.org.au |
| Looking at the documentation, I wonder whether it would be clearer to separate the breakpoints for UTI vs the ECOFFs when using for combination therapy - it's quite busy and difficult to read otherwise. I know this would be out of keeping with the formatting of the rest of the EUCAST CBPs, but the concept of using ECOFFs to decide whether the drug can be used as part of combination therapy is really quite different from the usual CBPs anyway, so it may be worth putting them in a different 'box' (rather than as Notes) anyway. |

| Responses: |
ECOFFs, when they are used by the laboratory for interpretation, are included in Notes columns throughout the Breakpoint Tables, not just for aminoglycosides. Creating a new “ECOFF” column would be a substantial change to these Tables, and is not considered warranted at this time. |

| Actions: None required |

| BSAC |
| Robin.howe@wales.nhs.uk |
| Mandy.wootton@wales.nhs.uk |
| The committee had significant concerns, as aminoglycosides have become important agents in antimicrobial stewardship drives to reduce the use of alternative broad-spectrum agents, reduce the spread of resistance and CDI. The committee does not accept that there is a strong signal in the literature of clinical failures of aminoglycosides. There is however evidence that the use of regimes including gentamicin can have a positive clinical outcomes and positive impact on resistance and CDI incidence (N.D. Ritchie et al. Restrictive antibiotic stewardship associated with reduced hospital mortality in gram-negative infection. QJM: An International Journal of Medicine, 2017, 155–161). However, the committee accepts that there should be warnings to alert clinical colleagues to the issue of using aminoglycosides as monotherapy for infections other than UTI. |

| Responses: |
Thank you for this thoughtful feedback. The point about how the ECOFFs should applied by the clinical laboratory is a good one. A pragmatic view is that the ECOFF is used as a breakpoint in laboratory information systems, and that for isolates outside the urinary tract (a blood isolate with an identical strain from urine being an exception) the warning about avoiding use as monotherapy be added to the report. A guidance document is planned to describe this. |

| Resulting from the discussion at the last |
In the UK, and probably elsewhere, aminoglycosides will continue to be used in combination regimes for infections outside the urinary tract. The current proposal does not really give laboratories clear guidance about how to report results to support use in this context. Having the guidance as a footnote means that laboratories will have to work out individual ways to produce reports, which will lead to local confusion, and be a challenge for national surveillance.

In order to give clear guidance, while retaining the cautionary notes, the BSAC Committee suggests that the ECOFF values given in the footnotes are transferred to the R column for each agent for the systemic indications. Recognising that high doses should be used, the committee suggests that, following the new convention for ‘Susceptible increased exposure, the S BP should be ≤0.001. Thus, organisms could be reported as I or R. The committee would retain the warning about the fact that aminoglycosides should be avoided as monotherapy for systemic infections. An example of the proposal for Enterobacterales is shown below.

The committee is concerned about the dosages given as standard and high dose for the aminoglycosides in general, but particularly for amikacin. It is unclear where both the standard dose (20mg/kg/day) and the high dose (30mg/kg) recommendations have come from. The BNF and SPC both specify 15mg/kg/day. A systematic review, published in 2016 by the BSAC Therapeutic Drug Monitoring working Party (Jenkins A et al. Amikacin use and therapeutic drug monitoring in adults: do dose regimens and drug exposures affect either outcome or adverse events? A systematic review. J Antimicrob Chemother. 2016 Oct;71(10):2754-9. doi: 10.1093/jac/dkw250. Epub 2016 Jul 11.) found that doses used in the literature ranged from 11-15 mg/kg/day, with 15mg/kg/day

Steering Committee meeting, there was also a decision that we will present the ECOFF-breakpoints for systemic use (combination therapy) in parenthesis, instead of just in the comment. A mock-up of this is being developed, and will be included in a new consultation where we will clarify better how labs should report for systemic use.

As for moving the ECOFFs to the “R” column, this is not needed as the footnotes will become a Note (Note 2 in fact) in the Notes column of the Breakpoint Tables to guide the laboratory. EUCAST is not recommending the use of high dose for isolates outside the urinary tract, so converting the “S” to “I” is not appropriate – rather this would again risk to cause confusion over the definition of “I”.

Others have also commented about the amikacin doses. The position of EUCAST is that doses lower than 20mg/kg/day will be inadequate based on the PK-PD.

**Actions:** Consistent with the proposals for all aminoglycosides, and with the PKPD of each agent, the dosages specified in the consultation document are required to give sufficient exposure to amikacin.
| Comments following Breakpoint Committee consultation on the wording of ‘combination’ therapy and the use of brackets for some breakpoints | Joseph Meletiadis  
University of Athens, Greece | I think the new way of presentation is clearer. However, since we introduce a new term, the bracketed BP, shouldn’t this be stated and defined somewhere in the BP table e.g. in Notes section and perhaps in guidance section? I am also a little bit concerned on the definition

“the breakpoint in brackets can be used to distinguish between wild type organisms and organisms with acquired resistance mechanisms”

which is actually a definition for an ECOFF not a BP. Why not this:

“the breakpoint in brackets are tentative breakpoints to be used only when aminoglycosides are given in combination with an active drug as PKPD breakpoints of aminoglycosides when given alone are much lower”

I understand that there are not many data to support a BP since aminoglycosides are always used in combination with other drugs and PK-PD BPs are determined when aminoglycosides are given alone. | EUCAST agrees with these points and will be ensuring they are dealt with appropriately when the new breakpoints are released with Breakpoint Tables 10.0 in January 2020 |