Guidance Document on Implementation and Use of the Revised Aminoglycoside Breakpoints

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Introduction
Following a detailed re-examination of aminoglycoside (AG) pharmacokinetics-pharmacodynamics and target attainment rates [1], EUCAST undertook an extensive review of aminoglycoside breakpoints. The EUCAST Steering Committee reviewed available literature focusing on AG efficacy when used in monotherapy [2], with the understanding that this would assist in revising breakpoints even though these agents are mostly used in combination with other antimicrobial classes.

It became apparent during the review that older dosing regimens had low target attainment rates against wild type species considered appropriate targets for AGs. Modern high-dose regimens are required to achieve coverage of most wild-type isolates, but even they sometimes fall short of complete coverage.

Use of the Revised Aminoglycoside Breakpoints

Systemic breakpoints
Systemic aminoglycosides are most often used for serious infections, including sepsis and severe sepsis. The revised breakpoints recognise that they are almost always prescribed in combination with antimicrobial agents in other classes when used for the treatment of systemic infections. This is reflected in the Breakpoint Tables by the use of Note 2 and the use of brackets to convey the fact that these are not true breakpoints, but ECOFF values for the purpose of interpretation of MIC values and inhibition zones to exclude isolates with acquired resistance mechanisms to respective agent.

Note 1/A
For systemic infections, aminoglycosides should be used in combination with other active therapy. In this circumstance, the value in brackets can be used to distinguish between wild type organisms and organisms with acquired resistance mechanisms.

“Other active therapy” can, for example, be another antimicrobial agent, surgical or other intervention, or any combination of these. However, it is important that the other antimicrobial, when used, should be known to be susceptible against the pathogen. EUCAST recommends the use of the text of Note 1/A as a report comment during and for a period after the laboratory implementation of the revised breakpoints.

Aminoglycoside dosing
Aminoglycoside dosing has undergone changes over the more than 50 years since the first agents were introduced. Initially, aminoglycosides were mainly given intramuscularly and administered three times daily. Gradually, IV administration was adopted and many started using twice daily and once daily injections. Doses of gentamicin, tobramycin and netilmicin increased from 3 mg/kg and day, to 4.5 and later to 6 or 7 mg/kg/day. The pharmacokinetic/pharmacokinetic modelling that underpins the new EUCAST aminoglycoside guidance used mg/kg of ideal body weight. Dosing using lean body weight or similar (using formulas based on height ± weight and actual body weight) as well as accounting for renal function is recommended [3].
Amikacin has over the years been dosed at 15, 20 and 25 mg/kg/day. However, given that amikacin is 4-fold less active than gentamicin, tobramycin and netilmicin but has the same PK-PD targets, the amikacin dose should be 4 times higher. This is more than is normally prescribed for amikacin and more than in any of the European or FDA guidelines [4-8]. EUCAST is concerned that doses lower than those listed here fail to deliver adequate exposure for the wild type populations of target species, especially in serious systemic infections. This is particularly problematic for amikacin where dosing traditions and acceptance is lower than for other aminoglycosides [9].

When using aminoglycosides in combination therapy with other antimicrobial agents, the evidence for successful use of lower doses is unclear; normally the goal in combination therapy is for each agent to be administered to achieve optimal drug exposure.

Breakpoints and dosing for infections originating in the urinary tract

Aminoglycosides are concentrated in urine and renal tissues. For this reason, is possible that lower doses are adequate for lower and uncomplicated upper urinary tract infections [5-8]. As with some other agents primarily used for serious infections, it is occasionally necessary to treat otherwise uncomplicated infections with an aminoglycoside because of resistance to other antimicrobial classes.

However, the appropriate dosing regimen for infections originating from the urinary tract is not established with any certainty, as most PK-PD data have been generated with the aim of using aminoglycosides for systemic infections (mouse thigh and lung models). While EUCAST attempts to determine the required dosages of gentamicin, tobramycin and amikacin for these infections, we suggest that a dose of at least 4.5 mg/kg/day of gentamicin and tobramycin or 20 mg/kg/day of amikacin are used.

Breakpoint Tables v 10.0

The revised breakpoints and dosages are based on known MIC distributions of relevant microorganisms and PK/PD calculations. Calculations assume that the aminoglycosides are being prescribed as monotherapy and that their doses are initial doses in seriously ill patients prior to therapeutic monitoring and dose adjustment. However, because these dosages are not listed in regulatory documents or used universally in clinical practice, EUCAST will undertake further detailed analyses with a view to refining dosages further.

References

4. Amikacin, gentamicin and tobramycin product labels at https://www.medicines.org.uk/emc
5. Amikacin, gentamicin and tobramycin product labels at https://labels.fda.gov/ingredientname.cfm