Guidance Document on Implementation and Use of the Revised Aminoglycoside Breakpoints

April 2020

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 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.

Results from a recent EUCAST survey show that:

- tobramycin is not available everywhere
- several countries are still using 3 mg/kg/day as standard dose of gentamicin and tobramycin, and

- amikacin dosage is most often 15 – 20 mg/kg/day, not the 25 – 30 mg/kg/day suggested by the pharmacokinetic/pharmacokinetic modelling and by the fact that amikacin is 4 times less active that gentamicin and tobramycin.

EUCAST is concerned that doses lower than those listed with the EUCAST breakpoints Dosages tab fail to deliver adequate exposure for the wild-type populations of target species, especially in serious systemic infections. This is particularly problematic foramikacin where dosing traditions are lower than in any European or FDA guideline [4 - 8] and acceptance of higher doses is lower than for other aminoglycosides [9]. EUCAST encourages the use of therapeutic drug monitoring for this drug class, which has a narrow window between efficacy and toxicity [9,10].

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 [3,10].

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 concentrated and bound in renal tissues. For this reason, it is possible that lower doses than those recommended for other infections 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).

EUCAST has reviewed published literature on the use of aminoglycosides in urinary tract infections, including infections arising from the urinary tract, in an attempt to determine the required dosages of gentamicin, tobramycin and amikacin for these infections. The results of this review are provided in the Appendix. In brief the evidence for the efficacy of lower doses is not of the required standard to answer the question.

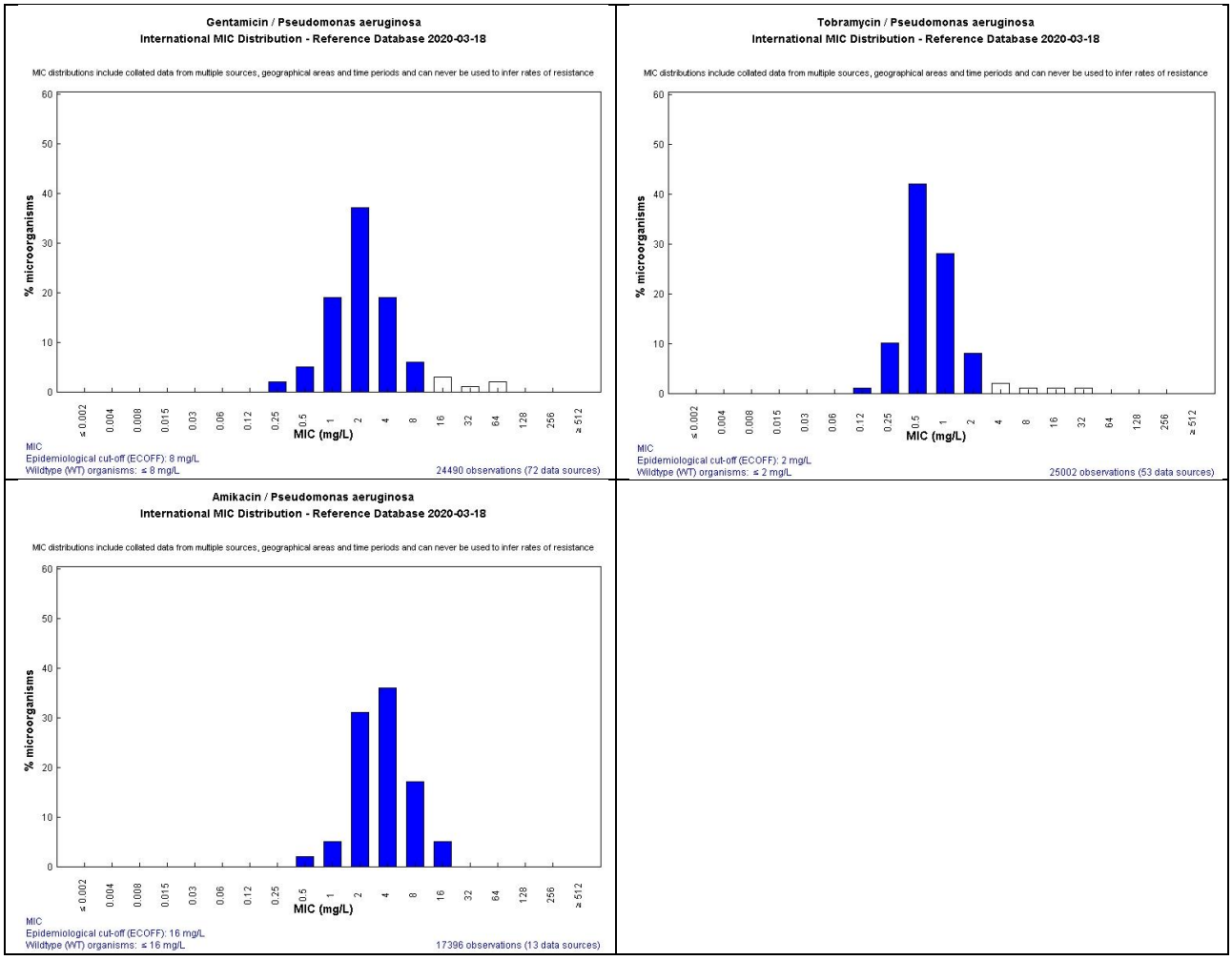
Breakpoint Tables v 10.0

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.

Aminoglycosides and *P. aeruginosa*

The activities of gentamicin, tobramycin and amikacin in relation to dose are comparable for most microorganisms but for *Pseudomonas aeruginosa* the activity of gentamicin is significantly weaker (ECOFF 8 mg/L) than that of the others (Figure). The dosing and PK-PD parameters for gentamicin and tobramycin are basically identical, so the two-fold lower MIC-values for tobramycin represent a true advantage over gentamicin. On the basis of available information, EUCAST has decided that the use of gentamicin for *P. aeruginosa* infections should be discouraged. Solid information on whether the activity of gentamicin is sufficient in uncomplicated urinary tract infections is not available. The ECOFFs of amikacin and tobramycin are 16 mg/L and 2 mg/L, respectively, but the difference is largely compensated for by doses being three to four times higher for amikacin (20 – 30 mg/kg/day vs. 6 – 7.5 mg/kg/day).

Figure: Aminoglycoside MIC distributions for *Pseudomonas aeruginosa*



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Appendix EUCAST Review of Aminoglycosides in Urinary Tract Infection

Question:	**As *monotherapy*, what doses of aminoglycosides are effective in the treatment of UTI, acute pyelonephritis and 'infections originating from the urinary tract?** **» In particular, can lower doses than those in our Dosages tab be used effectively?** **» Also, are lower doses satisfactory for bacteraemic UTI?**

Review:	Published literature, focusing on publications referenced in Vidal et al. (2007; aminoglycosides as monotherapy) and Jenkins et al. (2016; systematic review of amikacin dosing)

Results:	See Table below

Discussion and Conclusions

- » Many articles are so old that electronic access does not exist; We have not asked for inter-library loans or paid money for access (Karger for the latter)
- » Most studies are quite old, conducted at a time when lower doses were used, and endpoints differed, with many UTI studies reporting only bacteriological outcomes
- » Efficacy rates (based on failure rates) are not very encouraging for these lower doses
- » There are few studies with higher doses
- » The majority of studies were for treatment of complicated UTI, which may explain the lower than expected efficacy - relapses and reinfections clouding the picture
- » There are very limited data on acute pyelonephritis; the best (and most recent) study out of Korea failed to document doses
- » Most studies failed to document associated bacteraemia
- » It would be difficult to make any firm conclusions because none of the studies were directed at our questions
- » The evidence for the efficacy of lower doses is not of the required standard

Table Results of literature review: Part 1

First author	Year	Ref	Full paper?	Patient group	Agent	Dosing regimen	Total daily dose	Fail	N	Failure Rate	Pyelonephritis	Bacteraemia
Orange text = no electronic access to full paper												
VIDAL et al STUDIES												
Klastersky	1973	87	x	severe gnr infection in cancer	Gentamicin	?80 mg x 3	?320 mg (3.7-6.6 mg/kg)	1	4	25%	not stated	not stated
Ludwig	1980	92	Yes	acute recurrent and chronic UTIs	Gentamicin	80mg x 2	160mg	8	29	28%	not stated	not stated
Bernstein Hahn	1981	76	x	complicated UTIs	Gentamicin	not available	not available	9	18	50%	not stated	not stated
Seiler	1981	102	x	chronic UTIs	Tobramycin	80 mg single dose	80mg single dose	13	23	57%	not stated	not stated
Lentini	1982	90	x	complicated UTIs	Gentamicin	240mg im daily	240mg	9	20	45%	not stated	not stated
Abbruzzese	1983	71	Yes	various UTIs	Tobramycin	1 mg/kg x 3	3 mg/kg	10	33	30%	20 Fever; 11 Flank pain	3
Cox	1983	78	Yes	complicated UTIs	Tobramycin	1 mg/kg x 3	3 mg/kg	3	29	10%	not stated	0
Frimodt-Møller	1983	81	Yes	complicated UTIs	Tobramycin	1 mg/kg x 3	3 mg/kg	8	21	38%	not stated	not stated
Kleinschmidt	1983	88	x	acute cystitis	Gentamicin	120 mg single dose	120mg single dose	8	34	24%	not available	not available
Elder	1984	79	Yes	complicated UTIs	Gentamicin	1 mg/kg x 3	3 mg/kg	4	16	25%	0	not stated
					Tobramycin	1 mg/kg x 3	3 mg/kg	4	8	50%	0	
					Amikacin	5 mg/kg x 3	15 mg/kg					
Sattler	1984	101	Yes	serious UTIs	Gentamicin	1 mg/kg x 3?	3 mg/kg	3	13	18%	1	3
						1.7 mg/kg x 3?	5.1 mg/kg		4			
Bailey	1985	75	Yes	severe or complicated UTIs	Netilmicin	2 mg/kg x 2	4 mg/kg	1	16	6%	13	not stated
Bailey	1986	73	x	severe or complicated UTIs	Netilmicin	not available	not available	1	24	4%	not stated	not stated
Hahn	1987	84	x	complicated UTIs	Amikacin	not available	not available	11	22	50%	not available	not available
Lepage	1987	91	x	severe UTIs	Amikacin	500 mg x 1	500mg	3	20	15%	not available	not available
Hoepelman	1988	85	Yes	complicated UTIs	Gentamicin	1 mg/kg x 3	3 mg/kg	5	22	23%	2	not stated
Albertazzi	1989	72	x	reanl and urinary tract infections	Gentamicin	80mg x 2	160mg	33	92	36%	not available	not available
Gorski	1990	83	x	acute pyelonephritis	Gentamicin	not available	not available	10	33	30%	not available	not available
Bailey	1992	74	x	acute pyelonephritis	Netilmicin	not available	not available	4	19	21%	not available	not available
Waller	1992	105	Yes	serious UTIs	Gentamicin	80 mg x 3	240 mg	4	27	15%	3	not stated

Table Results of literature review: Part 2

First author	Year	Ref	Full paper?	Patient group	Agent	Dosing regimen	Total daily dose	Fail	N	Failure Rate	Pyelonephritis	Bacteraemia
Orange text = no electronic access to full paper												
OTHER STUDIES												
Madsen	1976	--	Yes	complicated UTIs	Tobramycin	1 mg/kg x 3	3 mg/kg	13	38	34%	not stated	not stated
					Gentamicin	2 mg/kg x 3	4 mg/kg	13	37	35%		
Gilbert	1977	--	Yes	UTIs (hospitalised)	Gentamicin	1-1.3 mg/kg x 3	3-4 mg/kg	9	15	60%	11	1
					Amikacin	3 mg/kg x 3	9 mg/kg	10	15	67%	11	2
Madsen	1977	--	Yes	complicated UTIs	Gentamicin	60 or 80 mg x 3	180 or 240 mg	18	49	37%	not stated	not stated
					Sisomicin	50 or 75 mg x 2	100 or 150 mg	15	50	30%		
Smith	1977	--	Yes	severe g-ve infections	Gentamicin	2 mg/kg x 3	6 mg/kg	25	32	78%	18 UTI	7
					Amikacin	8 mg/kg x 3	24 mg/kg	30	39	77%	24 UTI	5
Maigaard	1978	--	Yes	complicated UTIs	Netilmicin	2 mg/kg x 2	4 mg/kg	5	25	20%	not stated	not stated
					Amikacin	7.5 mg/kg x 2	15 mg/kg	3	19	16%		
Bock	1980	--	Yes	serious g-ve infections	Netilmicin	2 mg/kg x 3	6 mg/kg	0	15	0%	not stated	3/14 septicaemia failed
					Amikacin	7.5 mg/kg x 2	15 mg/kg	1	6	17%	not stated	2/17 septicaemia failed
Montgomerie	1982	--	Yes	spinal unjury UTI	Tobramycin	1 mg/kg x 3	3 mg/kg	8	13	62%	not stated	not stated
del Rosal	1983	--	Yes	serious infection	Gentamicin	1-1.7 mg/kg x 3	3-5 mg/kg	na	na	na	1	not stated
Penn	1983	--	Yes	complicated UTIs	Gentamicin	1 mg/kg x 3	3 mg/kg	10	23	43%	5	2
Whang	1984	--	x	severe surgical infections	Amikacin	450-500 mg x 2	900 -1000 mg	8	31	26%	not stated	not stated
LeFrock	1985	--	x	g-ve infectionot stated	Netilmicin	not available	not available			0.97	not stated	not stated
					Gentamicin	not available	not available			0.94		
Gudiol	1986	--	Yes	g-ve sepsis	Gentamicin	1.5 mg/kg x 3	4.5 mg/kg	1	13	4%	not stated	15/26 urinary origin
					Tobramycin	1.5 mg/kg x 4	4.5 mg/kg		13			
Sage	1987	--	Yes	serious sepsis	Netilmicin	2-3 mg/kg x 3	6-9 mg/kg	0	14	0%	14 UTI source	7
DeMaria	1989	--	Yes	serious g-ve infections	Tobramycin	1.5 mg/kg x 3	4.5 mg/kg	25	28	89%	not stated	not stated
					Amikacin	5 mg/kg x 3	15 mg/kg					
Noone	1989	--	Yes	severe infections	Netilmicin	3.5 mg/kg x 2	7 mg/kg	8	28	29%	34 urinary source	not stated
					Amikacin	7.5 mg/kg x 2	15 mg/kg	3	24	13%	28 urinary source	not stated
Paoletti	1989	--	x	lower UTI	Netilmicin	200 mg x 1	200 mg	na	na	na	not stated	not stated
Tammela	1990	--	Yes	serious infectionot stated urology pts	Tobramycin	1 mg/kg x 3	3 mg/kg	5	39	13%		12
Fang	1991	--	Yes	complicated UTIs	Gentamicin	1-1.7 mg/kg x 3	3-5 mg/kg	18	100	18%	not stated	not stated
Maller	1991	--	Yes	systemic infections	Amikacin	7.5 mg/kg x 2 or 15 mg/kg x 1	15 mg/kg	na	79	na	105/220	not stated
Melekos	1991	--	x	complicated UTIs	Amikacin	500 mg x 2	1000 mg	na	na	15%	not stated	not stated
Korvick	1992	--	Yes	*Klebsiella* bacteraemia	Gentamicin	not stated	not stated	10	46	22%	not stated	not stated
					Tobramycin	not stated	not stated	4	8	50%		
					Amikacin	not stated	not stated	0	6	0%		
Bailey	1996	--	x	acute pyelonephritis	Gentamicin	10 mg/kg	10 mg/kg	1	25	4%	25	not stated
					Gentamicin	2.5 mg/kg x 3?	?	3	16	19%	16	not stated
Wie	2014	--	Yes	acute pyelonephritis - 'complicated' non-obstructive	Gentamicin	not stated	not stated	3	275	1%	275	61