Amikacin	Rationale for the EUCAST clinical breakpoints, version 1.2	16th February, 2009

Introduction

The aminoglycosides are a group of naturally occurring or semi-synthetic compounds with bactericidal activity. Aminoglycoside therapy is relevant for severe or complicated infections caused by Enterobacteriaceae*, Pseudomonas* spp.*, Acinetobacter* spp. and staphylococci, all of which have been given clinical breakpoints. Monotherapy is not considered relevant in infections caused by *Streptococcus* spp. (including *Streptococcus pneumoniae*), *Enterococcus* spp.*, Neisseria* spp.*, Haemophilus* spp.*, Moraxella* spp. or anaerobic bacteria*.* In the case of *Enterococcus* spp. combination therapy with beta-lactam drugs may be synergistic unless the bacterium has acquired high level resistance to the aminoglycoside or the beta-lactam. Resistance to aminoglycosides is most commonly mediated by a range of plasmid encoded aminoglycoside-modifying enzymes. Various aminoglycosides have different susceptibility to modifying enzymes so resistance may not affect all aminoglycosides. Other resistance mechanisms include reduced permeability and modifications in ribosomal proteins or RNA.

EUCAST has determined clinical breakpoints for amikacin, gentamicin, netilmicin and tobramycin. They are with few exceptions available in all European countries. Aminoglycosides available only in few countries or in topical preparations have not been addressed.

Amikacin, gentamicin, netilmicin and tobramycin are active against the same groups of organisms which is why the same species or groups of species have received breakpoints for all four aminoglycosides. Tobramycin is marginally more potent against *Pseudomonas aeruginosa* than the other agents. Amikacin is active against some organisms with resistance to the other agents.

Gentamicin, netilmicin and tobramycin have sufficiently similar pharmacokinetic and pharmacodynamic properties to receive the same breakpoints throughout. The lower antibacterial activity of amikacin was considered to be compensated for by the pharmacokinetics of the drug.

Under-dosing of aminoglycosides is a major problem. The breakpoints suggested for aminoglycosides are based on modern once-daily administration of high aminoglycoside dosages. For gentamicin, netilmicin and tobramycin a daily dose of 4.5 – 7.5 mg/kg/day and for amikacin a daily dose of 15 – 20 mg/kg/day is considered appropriate. EUCAST has also considered the fact that most often aminoglycosides are given in combination with beta-lactam agents and that this is especially important in the therapy of *Pseudomonas* spp. infections.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	15-20 mg/kg/d	15 mg/kg	15 mg/kg/d	15mg/kg	-	15 mg/kg
Maximum dose schedule	15-20 mg/kg/d	1.5 g (adult)	15-20 mg/kg/d	-	-	15 mg/kg
Available formulations	Iv, im	iv, im	iv,im	iv, im	iv,im	Iv, im

2. MIC distributions and epidemiological cut-off (ECOFF) values

	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	ECOFF
Acinetobacter anitratus	0	0	0	0	0	0	0	0	4	31	61	44	17	13	16	0	0	0	0	8
Acinetobacter baumannii	0	0	0	0	0	0	0	0	23	227	648	474	210	122	138	16	4	28	0	8
Acinetobacter calcoaceticus	0	0	0	0	0	0	0	0	5	26	55	41	18	16	10	0	0	0	0	8
Acinetobacter lwoffii	0	0	0	0	0	0	0	0	74	87	45	25	13	6	9	0	0	0	0	8
Citrobacter freundii	0	0	0	0	0	0	0	1	27	347	573	132	34	22	19	2	0	0	0	8
Citrobacter koseri	0	0	0	0	0	0	0	0	66	234	158	25	5	0	2	0	0	0	0	8
Enterobacter aerogenes	0	0	0	0	0	0	0	0	23	391	943	270	112	58	35	4	0	1	0	8
Enterobacter cloacae	0	0	0	0	0	0	0	1	81	1807	2919	426	146	182	85	10	0	0	0	8
Enterobacter sakazakii	0	0	0	0	0	0	0	0	0	19	27	2	2	2	0	0	0	0	0	IE
Escherichia coli	0	0	0	1	0	0	0	16	129	1338	4008	1825	426	111	41	33	3	1	45	8
Haemophilus influenzae	0	0	0	0	0	0	0	0	5	7	184	670	830	98	5	0	0	0	0	16
Klebsiella oxytoca	0	0	0	0	0	0	0	0	53	1003	1063	283	51	29	6	4	0	0	0	8
Klebsiella pneumoniae	0	0	0	0	0	0	0	8	328	5067	4077	450	352	576	75	17	5	13	77	8
Klebsiella spp	0	0	0	0	0	0	0	0	8	60	13	1	0	0	0	0	0	0	0	8
Morganella morganii	0	0	0	0	0	0	0	6	26	111	107	41	17	3	0	3	0	0	0	8
Proteus mirabilis	0	0	0	0	0	0	0	8	51	380	1335	1522	557	123	22	5	1	3	0	8
Proteus spp	0	0	0	0	0	0	1	8	27	29	6	1	0	0	0	0	0	0	0	8
Proteus vulgaris	0	0	0	0	0	0	0	7	28	82	84	38	11	0	0	1	0	0	0	8
Providencia stuartii	0	0	0	0	0	0	0	0	1	2	6	1	0	0	0	0	0	0	0	IE
Pseudomonas aeruginosa	0	0	0	0	0	0	0	86	357	889	5026	5801	2683	939	79	103	11	0	0	16
Serratia marcescens	0	0	0	0	0	0	0	2	3	57	234	92	23	11	7	3	1	2	0	8
Staphylococcus aureus	0	0	0	0	0	0	0	17	62	209	1296	2234	883	301	76	62	0	0	0	8
Staphylococcus capitis	0	0	0	0	0	0	0	39	59	35	6	5	6	0	1	2	0	0	0	IE
Staphylococcus epidermidis	0	0	0	0	0	0	0	40	320	508	294	185	192	132	77	279	1	1	0	IE
Staphylococcus haemolyticus	0	0	0	0	0	0	0	17	23	25	67	62	111	37	14	30	1	0	1	IE
Staphylococcus hominis	0	0	0	0	0	0	0	10	63	47	101	59	30	8	5	12	0	0	0	IE
Staphylococcus warnerii	0	0	0	0	0	0	0	5	16	28	10	6	3	0	0	1	1	0	0	IE

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence (IE) no epidemiological cut-off has been determined.

3. Breakpoints prior to harmonisation (mg/L) S≤ R>						
	BSAC	**CA-SFM**	**CRG**	**DIN**	**NWGA**	**SRGA**
General breakpoints	-	8/16	4/16	4/32	-	8/8
Species related breakpoints						
Staphylococci	4/16					4/4
Streptococci						8/8
S. pneumoniae						8/8
Enterococci						8/8
Corynebacteria						
Enterobacteriaceae	4/4	8/16				4/4
Pseudomonas spp.	4/16	8/16				8/8
Acinetobacter spp.	4/4	8/16				4/4
Haemophilus/Moraxella spp.						
N.meningitidis						
N.gonorrhoeae						
P.multocida						
Anaerobes						
Campylobacter spp.						
Helicobacter pylori						

4. Pharmacokinetics				
Dosage	7.5 mg/kg			
Cmax (mg/L)	24			
Cmin (mg/L)	5			
Total body clearance (L/h)	-			
T ½ (h), mean (range)	2 – 3			
AUC24h (mg.h/L)	-			
Fraction unbound (%)	>90			
Volume of distribution (L/kg)	0.3			
Comments	• The drug is not metabolised. • Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Van der Auwera P. J Antimicrob Chemother 1991; 27 (Suppl C):63-71. • Edson RS, Terrell CL. Mayo Clin Proc 1991; 66):1158-64.			

5. Pharmacodynamics				
*f*AUC/MIC for bacteriostasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Under review.			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

No data available.

7. Clinical data

Aminoglycosides should be used in combination with other agents, with the exception of urinary tract infections. There is extensive clinical experience that target infections with Enterobacteriaceae, *Pseudomonas aeruginosa* and, to a lesser extent, staphylococci without aminoglycoside resistance mechanisms respond clinically to aminoglycosides. For streptococci and enterococci without high level resistance to aminoglycosides, there may be enhanced bactericidal activity when aminoglycosides are used in combination with cell wall inhibitors (beta-lactams and glycopeptides).

8. Clinical breakpoints	
Non-species-related breakpoints	In the absence of Pk/Pd data these have been determined mainly on the basis of Pk data and pre-existing breakpoints. The column of non-species related breakpoints is for use only for species not included in the table. Breakpoints are S≤8 mg/L, R>16 mg/L. These breakpoints render wild type Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp and *Staphylococcus* spp. susceptible to amikacin.
Species-related breakpoints	
Species without breakpoints	*Enterococcus* spp., *Streptococcus* spp.and anaerobic bacteria were considered poor targets for amikacin therapy and for that reason did not receive breakpoints. Aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and beta-lactams against enterococci without acquired resistance mechanisms. There is no synergistic effect against enterococci with high level aminoglycoside resistance. *Haemophilus* spp. and *Moraxella* spp. were considered possible targets for amikacin therapy but the evidence was considered insufficient to set breakpoints.
Clinical qualifications	
Dosage	EUCAST breakpoints apply to intravenous amikacin dosage of 15 mg/kg/day.
Additional comment	

9. Amikacin - EUCAST clinical MIC breakpoints

These can be found at **http://www.eucast.org**

10. Exceptions noted for individual national committees

None