Tobramycin	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	4.5 mg/kg x 1	3 mg/kg x 1	3-7 mg/kg x 1	3-6mg/kg x 1	3-5 mg/kg x 1	3 – 6 mg/kg x 1
Maximum dose schedule	6-7 mg/kg x 1	5 mg/kg x 1	5 mg/kg x 2	6mg/kg x 1	5 mg/kg x 1	7,5 mg/kg x 1
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	5	44	56	35	13	11	15	0	0	0	0	0	4
Acinetobacter baumannii	0	0	0	0	0	1	10	154	835	989	501	234	204	260	31	28	14	40	13	4
Acinetobacter calcoaceticus	0	0	0	0	0	0	0	8	45	58	29	15	18	17	2	1	0	0	0	4
Acinetobacter lwoffii	0	0	0	0	0	0	60	93	87	44	18	13	12	19	1	2	2	4	0	2
Acinetobacter spp	0	0	0	0	1	5	8	145	165	135	40	18	15	8	7	7	0	0	26	4
Aeromonas hydrophila	0	0	0	0	0	0	0	0	2	2	0	0	0	0	1	0	0	0	0	IE
Burkholderia cepacia	0	0	0	0	0	0	1	0	1	0	6	2	2	11	4	4	6	3	0	IE
Citrobacter freundii	0	0	0	0	0	1	11	103	851	633	184	53	66	81	25	8	1	0	36	2
Citrobacter koseri	0	0	0	0	0	2	4	160	250	97	22	2	1	3	2	0	0	0	0	2
Citrobacter spp	0	0	0	0	0	0	0	23	161	189	68	9	6	5	3	3	1	1	45	2
Enterobacter aerogenes	0	0	0	0	0	0	10	127	1035	724	170	19	51	112	4	3	0	2	53	2
Enterobacter cloacae	0	0	0	0	0	9	38	526	4160	2344	394	86	115	235	48	20	1	0	63	2
Enterobacter sakazakii	0	0	0	0	0	0	0	5	20	19	4	1	1	0	0	0	0	0	0	2
Enterobacter spp	0	0	0	0	0	1	1	16	256	492	142	16	6	7	10	8	3	0	79	2
Enterococcus faecalis	0	0	0	10	0	2	2	2	5	2	12	53	184	305	65	42	55	6	0	32
Enterococcus faecium	0	0	0	0	0	0	0	0	0	0	2	2	2	9	16	16	20	9	0	32
Escherichia coli	0	0	0	1	5	5	43	954	8503	11475	3975	818	402	301	199	99	6	0	70	2
Haemophilus influenzae	0	0	0	0	0	0	0	2	27	167	674	949	36	0	0	0	0	0	0	8
Hafnia alvei	0	0	0	0	0	1	9	9	5	2	0	0	0	0	0	0	0	0	0	IE
Klebsiella oxytoca	0	0	0	0	0	2	17	539	2059	1312	285	66	59	56	15	8	3	0	85	2
Klebsiella ozaenae	0	0	0	0	0	0	0	4	7	4	2	2	0	1	0	0	0	0	0	IE
Klebsiella pneumoniae	0	0	0	1	1	8	81	1979	7057	3109	615	173	289	565	114	46	7	0	94	2
Klebsiella spp	0	0	0	0	0	0	0	6	29	2	1	1	0	0	1	1	0	0	0	2
Morganella morganii	0	0	0	0	0	1	17	174	402	277	77	24	10	3	4	4	0	0	100	4
Proteus mirabilis	0	0	1	1	0	6	3	330	1994	2509	1089	405	189	138	20	4	0	2	125	4
Proteus spp	0	0	0	0	0	3	4	23	18	15	5	4	0	0	0	0	0	0	0	4
Proteus vulgaris	0	0	0	1	0	0	9	111	344	290	80	13	10	5	1	1	0	0	133	4
Pseudomonas aeruginosa	0	0	0	0	1	3	324	2429	9794	6532	1834	473	311	420	289	180	39	0	112	2

	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	
Serratia liquefaciens	0	0	0	0	0	0	0	17	35	64	35	13	1	4	2	0	0	0	144	4
Serratia marcescens	0	0	0	0	1	1	6	34	189	471	500	133	42	21	14	7	8	6	161	4
Serratia spp	0	0	0	0	0	0	0	3	22	68	113	35	4	3	1	0	0	0	175	4
Staphylococcus aureus	0	0	0	6	24	32	168	286	688	206	59	17	18	44	14	13	7	3	0	1
Staphylococcus capitis	0	0	0	4	2	1	2	2	7	0	4	0	2	1	0	0	0	0	3	IE
Staphylococcus coagulase negative	0	0	0	0	8	17	35	119	51	2	1	19	23	33	22	26	42	22	0	0.5
Staphylococcus epidermidis	0	0	0	21	14	45	37	24	38	13	27	24	24	27	25	11	15	39	0	IE
Staphylococcus haemolyticus	0	0	1	3	2	1	1	0	6	2	2	5	1	4	1	0	13	2	2	IE
Staphylococcus hominis	0	0	1	1	9	5	1	5	5	1	6	2	0	2	2	1	0	1	1	IE
Staphylococcus lugdunensis	0	0	0	2	2	2	1	4	1	1	0	0	0	2	2	1	0	0	0	IE
Staphylococcus saprophyticus	0	0	0	12	10	4	3	2	0	0	0	0	0	0	0	0	0	0	0	IE
Staphylococcus warnerii	0	0	0	1	3	3	2	0	1	0	0	2	3	0	0	1	1	0	4	IE
Streptococcus pneumoniae	0	0	0	2	1	0	1	3	10	39	2	13	72	122	51	10	3	3	0	IE
Streptococcus pyogenes	0	0	0	2	2	0	2	2	10	18	6	23	44	47	15	0	0	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	CLSI
General breakpoint							
		4/8	1/4	1/8	2/4	4/4	
Species specific breakpoints:							
Enterobacteriaceae	1/1	4/8			2/4	2/2	4/8
Pseudomonas spp.	1/4	4/8			4/4	4/4	4/8
Acinetobacter spp.	1/1	4/8			2/4	2/2	4/8
Staphylococcus spp.	1/1	4/8			2/4	1/1	4/8
Streptococcus spp.					excluded	1/1	excluded
S. pneumoniae					excluded	1/1	excluded
Enterococcus spp.						1/1	see gentamicin
Haemophilus/Moraxella spp.							excluded
Corynebacteria					IE	IE	
N. meningitidis							excluded
N. gonorrhoeae							excluded
P. multocida							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
Campylobacter spp.					excluded	excluded	
Helicobacter pylori		4/8					

4. Pharmacokinetics

Dosage (mg)	1 mg/kg	2 mg/kg		
Cmax (mg/L)	4- 6 mg/L	10-12 mg/L		
Cmin (mg/L)	<1	1-2		
Total body clearance (L/h)				
T ½ (h), mean (range)	1.5 – 3 h	1.5 – 3h		
AUC24h (mg.h/L)				
Fraction unbound (%)	>90	>90		
Volume of distribution (L/Kg)	0.3	0.3		
Comments	• The drug is not absorbed from the intestine, is not metabolised and is excreted through glomerular filtration • Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Winslade NE et al. Antimicrob Agents Chemother 1987; 31:605-9.			

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≤2 mg/L, R>4 mg/L. These breakpoints render wild type Enterobacteriaceae and *Staphylococcus* spp. susceptible to tobramycin.
Species-related breakpoints	For *Pseudomonas* spp. and *Acinetobacter* spp., the S/I breakpoint was increased from S≤2 mg/L to S≤4 mg/L to avoid dividing the wild type MIC distribution.
Species without breakpoints	*Enterococcus* spp.*, Streptococcus* spp. and anaerobic bacteria were considered poor targets for tobramycin 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 tobramycin therapy but the evidence was considered insufficient to set breakpoints.
Clinical qualifications	
Dosage	EUCAST breakpoints apply to intravenous tobramycin dosage of 3-4.5 mg/kg/day.
Additional comment	

9. Tobramycin - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None