

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	3-6 mg/kg x 1	3 – 6 mg/kg x 1
Maximum dose schedule	6-7 mg/kg x 1	6 mg/kg x 1	5 mg/kg x 2	7,5mg/kg x 1	6 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
<i>Acinetobacter anitratus</i>	0	0	0	0	0	0	0	6	29	37	25	7	5	7	0	0	0	0	0	4
<i>Acinetobacter baumannii</i>	0	0	0	0	0	2	15	197	580	548	289	188	174	102	37	67	24	85	7	4
<i>Acinetobacter calcoaceticus</i>	0	0	0	0	0	0	0	6	24	32	21	16	13	7	0	0	0	0	0	4
<i>Acinetobacter lwoffii</i>	0	0	0	0	0	1	0	0	14	3	1	3	0	4	0	0	0	0	0	IE
<i>Acinetobacter</i> spp.	0	0	0	2	6	16	55	51	56	39	17	5	4	5	12	13	4	2	2	IE
<i>Aeromonas hydrophila</i>	0	0	0	0	0	0	0	1	8	3	0	1	0	0	0	1	0	0	0	IE
<i>Alcaligenes xylosoxidans</i>	0	0	0	0	0	0	0	0	2	0	2	3	2	12	3	2	0	1	0	IE
<i>Campylobacter coli</i>	0	0	0	0	3	7	24	727	897	431	97	2	1	0	0	0	0	0	0	2
<i>Campylobacter jejuni</i>	0	0	0	0	7	18	116	778	292	115	19	0	1	0	0	0	0	0	0	1
<i>Citrobacter freundii</i>	0	0	0	1	0	0	17	269	798	363	56	36	37	93	15	55	1	0	32	2
<i>Citrobacter koseri</i>	0	0	0	0	0	2	8	41	137	52	12	2	3	1	0	0	1	0	0	2
<i>Citrobacter</i> spp.	0	0	0	0	0	0	1	95	274	125	18	3	5	0	5	11	1	0	41	2
<i>Enterobacter aerogenes</i>	0	0	0	0	1	0	7	109	660	508	100	35	29	9	2	12	2	13	48	2
<i>Enterobacter amnigenus</i>	0	0	0	0	0	0	0	2	4	1	1	0	0	0	0	0	0	0	0	IE
<i>Enterobacter cloacae</i>	0	0	0	0	0	8	36	817	2999	1266	135	71	99	75	9	73	26	29	58	2
<i>Enterobacter gergoviae</i>	0	0	0	0	0	0	0	2	3	2	0	0	0	0	0	0	0	0	0	IE
<i>Enterobacter intermedium</i>	0	0	0	0	0	0	0	1	2	0	0	0	0	1	0	0	0	0	0	IE
<i>Enterobacter sakazakii</i>	0	0	0	0	0	0	0	6	14	7	3	0	1	0	0	0	0	0	0	IE
<i>Enterobacter</i> spp.	0	0	0	0	0	1	5	205	655	297	34	12	5	6	5	11	7	4	75	2
<i>Enterobacter taylorae</i>	0	0	0	0	0	0	0	0	3	1	0	0	0	0	0	0	0	0	0	IE
<i>Enterococcus faecalis</i>	0	0	0	0	0	2	2	5	18	36	71	159	650	1500	660	57	57	44	543	32
<i>Enterococcus faecium</i>	0	0	0	1	0	0	1	3	4	9	21	224	422	268	44	5	1	20	216	32
<i>Escherichia coli</i>	0	0	4	3	18	40	386	5857	16128	9077	1774	428	288	418	319	398	71	118	68	2
<i>Haemophilus influenzae</i>	0	0	0	0	0	0	0	10	19	52	26	7	0	0	0	0	0	0	0	4
<i>Hafnia alvei</i>	0	0	0	0	0	0	3	11	13	1	0	0	0	0	0	0	0	0	0	IE
<i>Klebsiella oxytoca</i>	0	0	1	0	0	2	10	548	1773	741	119	47	33	24	9	33	3	6	83	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	ECOFF
<i>Klebsiella pneumoniae</i>	0	0	2	2	3	5	104	1386	4979	1846	249	205	243	244	113	129	116	143	91	2
<i>Klebsiella</i> spp.	0	0	0	1	5	5	69	405	481	191	10	2	7	4	5	5	5	4	0	2
<i>Mannheimia haemolytica</i>	0	0	0	0	0	0	0	1	2	70	66	4	0	0	2	2	0	0	0	4
<i>Moraxella catarrhalis</i>	0	0	0	0	2	12	27	0	1	0	0	0	0	0	0	0	0	0	0	IE
<i>Morganella morganii</i>	0	0	0	0	0	2	19	229	478	286	67	31	12	25	17	22	5	6	97	2
<i>Pasteurella multocida</i>	0	0	0	0	0	2	4	3	16	88	107	21	2	6	60	43	4	0	0	4
<i>Proteus mirabilis</i>	0	0	0	0	1	4	20	543	1807	2166	992	229	118	189	49	133	20	16	123	2
<i>Proteus</i> spp	0	0	0	0	0	3	5	31	43	26	14	1	1	0	0	0	0	2	0	2
<i>Proteus vulgaris</i>	0	0	0	0	0	3	35	188	335	204	57	20	5	12	3	6	3	2	130	2
<i>Providencia rettgeri</i>	0	0	0	0	0	0	0	1	0	2	1	1	0	0	0	1	0	1	0	IE
<i>Providencia stuartii</i>	0	0	0	0	0	0	0	0	3	2	2	5	3	3	2	0	3	2	0	IE
<i>Pseudomonas aeruginosa</i>	0	0	0	0	2	3	44	383	1102	3546	7987	4079	1339	682	261	478	41	19	115	8
<i>Salmonella</i> spp.	0	0	0	0	0	0	77	6881	4668	770	90	8	10	46	48	23	1	0	0	1
<i>Serratia liquefaciens</i>	0	0	0	0	0	0	0	45	76	37	5	3	2	2	0	1	0	0	139	2
<i>Serratia marcescens</i>	0	0	0	0	0	2	17	117	776	393	54	21	32	39	54	19	8	50	156	2
<i>Serratia</i> spp.	0	0	0	0	0	0	1	34	198	188	41	6	6	10	17	11	5	0	169	2
<i>Staphylococcus aureus</i>	0	0	0	5	29	61	1933	10629	16730	8185	1576	343	339	628	1103	106	271	114	287	2
<i>Staphylococcus capitis</i>	0	0	0	3	5	3	2	5	7	0	2	0	0	4	0	0	0	0	3	IE
<i>Staphylococcus coagulase negative</i>	0	0	0	11	47	188	195	139	12	6	24	24	82	138	124	149	97	28	5	0.5
<i>Staphylococcus epidermidis</i>	0	0	0	26	39	425	89	30	52	7	27	64	86	90	156	93	30	1	0	0.5
<i>Staphylococcus haemolyticus</i>	0	0	3	1	5	51	6	2	9	2	5	4	37	28	23	40	31	3	3	0.5
<i>Staphylococcus hominis</i>	0	0	0	7	11	6	3	4	4	2	4	2	2	1	2	0	0	0	1	IE
<i>Staphylococcus intermedius</i>	0	0	0	0	0	0	0	41	54	4	0	0	0	0	0	0	0	0	0	IE
<i>Staphylococcus lugdunensis</i>	0	0	0	0	2	4	1	5	1	0	0	1	0	0	1	0	0	0	0	IE
<i>Staphylococcus saprophyticus</i>	0	0	0	14	6	2	3	1	0	1	0	0	0	1	0	1	0	0	0	IE
<i>Staphylococcus warnerii</i>	0	0	0	1	2	7	2	0	0	0	1	1	2	0	0	0	1	0	4	IE
<i>Streptococcus agalactiae</i>	0	0	2	0	3	4	1	0	3	1	7	9	49	194	85	37	18	7	0	IE
<i>Streptococcus anginosus</i>	0	0	0	0	0	0	0	0	0	0	1	2	16	9	1	1	0	0	0	IE
<i>Streptococcus</i> group G	0	0	0	1	1	0	0	0	1	1	8	42	27	3	1	0	0	0	0	IE
<i>Streptococcus intermedius</i>	0	0	0	0	0	0	0	0	0	0	1	2	6	5	1	0	0	0	0	IE

	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
<i>Streptococcus oralis</i>	0	0	0	0	0	0	0	0	1	1	3	7	6	5	20	8	0	0	0	IE
<i>Streptococcus pneumoniae</i>	0	0	0	0	3	7	6	22	15	50	39	159	296	277	517	234	5	1	230	IE
<i>Streptococcus pyogenes</i>	0	0	0	0	1	2	2	4	7	33	105	616	1396	286	39	7	0	0	237	IE
<i>Streptococcus viridans</i> group	0	0	0	0	0	0	0	0	1	3	12	19	30	73	26	34	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	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
<i>Pseudomonas</i> spp.	1/4	4/8			4/4	4/4	4/8
<i>Acinetobacter</i> spp.	1/1	4/8			2/4	2/2	4/8
<i>Staphylococcus</i> spp.	1/1	4/8			2/4	1/1	4/8
<i>Streptococcus</i> spp.		250/500				1/1	excluded
<i>S. pneumoniae</i>		250/500				1/1	excluded
<i>Enterococcus</i> spp.		4/8			512/512	1/1	≥500
<i>Haemophilus/Moraxella</i> spp.		2/4			excluded	excluded	excluded
Corynebacteria					IE	IE	
<i>N. meningitidis</i>					excluded	excluded	excluded
<i>N. gonorrhoeae</i>					excluded	excluded	excluded
<i>P. multocida</i>					excluded	excluded	
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.					excluded	excluded	
<i>Helicobacter pylori</i>		4/8					

4. Pharmacokinetics

Dosage (mg)	1 mg/kg	2 mg/kg		
Cmax (mg/L)	4 – 6	12		
Cmin (mg/L)	<1	1-2		
Total body clearance (L/h)				
T ½ (h), mean (range)	1.5 – 3	1.5 - 3		
AUC24h (mg.h/L)				
Fraction unbound (%)	>90	>90		
Volume of distribution (L/kg)	0.18-0.25	0.18-0.25		
Comments	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Demczar DJ, Nafziger AN, Bertino JS Antimicrob Agents Chemother 1997; 41:1115-9.• Meunier F et al. J Antimicrob Chemother 1987; 19:225-31.			

5. Pharmacodynamics

fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none">• 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	<p>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.</p> <p>Breakpoints are $S \leq 2$ mg/L, $R > 4$ mg/L. These breakpoints render wild type Enterobacteriaceae and <i>Staphylococcus</i> spp. susceptible to gentamicin.</p>
Species-related breakpoints	<p>For <i>Pseudomonas</i> spp. and <i>Acinetobacter</i> spp., the S/I breakpoint was increased from $S \leq 2$ mg/L to $S \leq 4$ mg/L to avoid dividing the wild type MIC distribution.</p>
Species without breakpoints	<p><i>Enterococcus</i> spp., <i>Streptococcus</i> spp. and anaerobic bacteria were considered poor targets for gentamicin therapy and for that reason did not receive breakpoints.</p> <p>Aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and beta-lactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gentamicin MIC > 128 mg/L.</p> <p><i>Haemophilus</i> spp. and <i>Moraxella</i> spp. were considered possible targets for gentamicin therapy but the evidence was considered insufficient to set breakpoints.</p>
Clinical qualifications	
Dosage	<p>Breakpoints apply to intravenous gentamicin dosage of 3-4.5 mg/kg/day.</p>
Additional comment	

9. Gentamicin - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees
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None
