

## 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

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>
Most common dose	4-5 mg/kg x 1	4-6 mg/kg x 1	3-7 mg/kg x 1	4-6mg/kg x 1	4-6 mg/kg x 1	4-6 mg/kg x 1
Maximum dose schedule	6-7 mg/kg x 1	7.5 mg/kg x 1	5 mg/kg x 2	7,5mg/kg x 1	6 mg/kg x 1	6-7.5 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</i> spp	0	0	0	2	3	5	13	7	9	5	1	0	1	0	4	0	0	0	0	IE
<i>Enterobacter</i> spp	0	0	0	0	1	1	2	31	62	7	3	6	1	1	0	0	0	0	0	IE
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	1	6	5	8	9	17	135	146	71	12	0	IE
<i>Escherichia coli</i>	0	0	0	0	0	0	6	1354	1904	733	218	77	47	19	15	8	0	0	0	2
<i>Klebsiella</i> spp	0	0	0	0	0	0	1	76	87	9	4	0	0	0	0	0	0	0	0	2
<i>Proteus mirabilis</i>	0	0	0	0	0	0	0	7	57	53	25	2	2	0	0	0	0	0	0	4
<i>Proteus</i> spp	0	0	0	0	0	0	6	30	57	15	12	4	2	0	0	0	0	0	0	IE
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	0	3	5	48	139	82	23	10	5	0	0	4	0	0	4
<i>Staphylococcus aureus</i>	0	0	0	0	0	1	9	12	5	3	3	4	1	1	1	0	0	0	0	1
<i>Staphylococcus capitis</i>	0	0	0	1	0	0	0	0	0	0	2	1	0	0	0	0	0	0	3	IE
<i>Staphylococcus coagulase negative</i>	0	0	0	1	3	16	4	1	1	5	6	2	1	0	0	0	0	0	0	IE
<i>Staphylococcus epidermidis</i>	0	0	0	0	3	16	17	3	0	3	13	23	11	30	5	4	0	2	0	IE
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	0	0	0	0	0	1	2	6	4	0	0	2	4	2	IE
<i>Staphylococcus hominis</i>	0	0	0	2	1	3	1	0	2	0	1	0	0	0	0	0	0	0	1	IE
<i>Staphylococcus saprophyticus</i>	0	0	0	12	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	IE
<i>Staphylococcus warnerii</i>	0	0	0	1	3	5	3	0	0	2	2	0	0	1	0	0	0	0	4	IE
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	120	0	0	IE
<i>Streptococcus agalactiae</i>	0	0	0	0	0	0	0	0	0	0	0	0	3	11	5	1	0	0	0	IE
<i>Streptococcus pneumoniae</i>	0	0	0	0	0	0	0	0	0	0	0	4	8	7	3	2	1	0	0	IE
<i>Streptococcus viridans</i> group	0	0	0	0	0	0	0	0	0	2	6	10	3	4	0	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<sub>≤</sub> R<sub>></sub>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoint</b>							
		4/8	2/8	1/8	2/4	4/4	
<b>Species specific breakpoints:</b>							
Enterobacteriaceae	1/1	4/8			2/4	2 / 2	8/16
<i>Pseudomonas</i> spp.	1/4	4/8			4/4	4 / 4	8/16
<i>Acinetobacter</i> spp.		4/8			2/4	2 / 2	8/16
<i>Staphylococcus</i> spp.	1/1				2/4	1 / 1	8/16
<i>Streptococcus</i> spp.					excluded	1 / 1	excluded
<i>S. pneumoniae</i>					excluded	1 / 1	excluded
<i>Enterococcus</i> spp.						1 / 1	see gentamicin
<i>Haemophilus/Moraxella</i> spp.							excluded
Corynebacteria							excluded
<i>N. meningitidis</i>							excluded
<i>N. gonorrhoeae</i>					excluded	excluded	excluded
<i>P. multocida</i>					excluded	excluded	
Anaerobes, Gram-positive					excluded		
Anaerobes, Gram-negative					excluded		
<i>Campylobacter</i> spp.					excluded	excluded	
<i>Helicobacter pylori</i>		4/8					
<i>Bacillus anthracis</i>					excluded	excluded	excluded

#### 4. Pharmacokinetics

Dosage (mg)	4-6 mg/kg			
Cmax (mg/L)	10-15			
Cmin (mg/L)	<1			
Total body clearance (L/h)				
T ½ (h), mean (range)	1.5-3			
AUC24h (mg.h/L)				
Fraction unbound (%)	≥70			
Volume of distribution (L/kg)	0.18-0.25			
Comments	<ul style="list-style-type: none"><li>• The drug is not absorbed from the intestine, is not metabolised and is excreted through glomerular filtration</li><li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li></ul>			
References	<ul style="list-style-type: none"><li>• Craig WA, Gudmundsson S, Reich RM. Pharmacotherapy. 1983; 3:305-15.</li><li>• Kahlmeter G. Scand J Infect Dis Suppl 1980; Suppl 23:74-81.</li></ul>			

## 5. Pharmacodynamics

<i>f</i> AUC/MIC for bacteriostasis				
<i>f</i> AUC/MIC for 2 log reduction				
<i>f</i> AUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"><li>• Under review.</li></ul>			
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 <math>S \leq 2</math> mg/L, <math>R &gt; 4</math> mg/L. These breakpoints render wild type Enterobacteriaceae and <i>Staphylococcus</i> spp. susceptible to netilmicin.</p>
Species-related breakpoints	<p>For <i>Pseudomonas</i> spp. and <i>Acinetobacter</i> spp., the S/I breakpoint was increased from <math>S \leq 2</math> mg/L to <math>S \leq 4</math> 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 netilmicin 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 against enterococci without acquired resistance mechanisms. There is no synergistic effect against enterococci with high level aminoglycoside resistance.</p> <p><i>Haemophilus</i> spp. and <i>Moraxella</i> spp. were considered possible targets for netilmicin therapy but the evidence was considered insufficient to set breakpoints.</p>
Clinical qualifications	
Dosage	<p>Breakpoints apply to intravenous netilmicin dosage of 4-6 mg/kg/day.</p>
Additional comment	

## 9. Netilmicin - EUCAST clinical MIC breakpoints

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

<b>10. Exceptions noted for individual national committees</b>
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