

Netilmicin: Rationale for EUCAST Clinical Breakpoints

Current version	2.0	September 2023
Previous versions	1.0	February 2009

Introduction

Netilmicin is a member of the aminoglycoside group of antimicrobial agents. 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 *Enterobacterales*, *Pseudomonas* spp., *Acinetobacter* spp., all of which have been given clinical breakpoints. Monotherapy is not considered relevant in infections caused by *Staphylococcus* spp., *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.

Amikacin, gentamicin, tobramycin and netilmicin are mostly active against the same groups of organisms which is why most species or groups of species have received breakpoints for all three aminoglycosides. Tobramycin is significantly more potent against *Pseudomonas aeruginosa* than the other agents, whereas gentamicin and netilmicin have the lowest activity against this species.

Gentamicin, netilmicin and tobramycin have sufficiently similar pharmacokinetic and pharmacodynamic properties to receive the same breakpoints throughout. The higher MICs of amikacin are 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 6-7 mg/kg/day and for amikacin a daily dose of 25-30 mg/kg/day is considered appropriate. Despite using high-dose therapy, the aminoglycosides are not sufficiently active to be used in monotherapy of infections, except those emanating from the urinary tract. When used in combination with other active therapy, the aminoglycosides can also be used for other systemic infections.

This version is extracted and updated from version 1.0 and will be the format for future updates. Previous versions are available on request.

Dosages related to clinical breakpoints

Standard dosage: 6-7 mg/kg x 1

High dosage: None

MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

Pharmacokinetics

PK parameter	Pharmacological studies		Clinical studies		Cancer patients ^e
	Healthy ^a	Healthy ^b	Infected patients ^c	Urology patients ^d	
Dosage	2.5 mg/kg	1 mg/kg	2.5-5.0 mg/kg/day	100 mg	Not stated
C _{max} (mg/L)	9.50 ± 1.48				
C _{min} (mg/L)					
Total body clearance (L/h)		2.90 ± 0.65		4.2 ± 1.6	3.32 ± 1.08
T _{1/2} (h), range	2.54 ± 0.47	2.68 ± 1.09		1.61 ± 0.66	2.98 ± 1.06
AUC ₀₋₁₂ (mg.h/L)	44.40 ± 6.86				
AUC ₀₋₂₄ (mg.h/L)					
AUC _{0-∞} (mg.h/L)	46.37 ± 7.89				
Fraction unbound (%)			<3*		
Volume of distribution		V _{ss} 2.01 ± 1.45 L/kg	V _c = 19.3 ± 5.8 L		12.8 ± 1.0 L

^a Chung et al., AAC 1980; 17:1894-7

^b Winslade et al., AAC 1987; 31:605-9

^c Edwards et al, AAC 1981; 20:714-7

^d Jauregizar et al., BJCP 2003; 55:552-9

^e Chang et al., BJCP 2009; 48:33-5

*Gialdroni-Grassi et al., 1978 (protein binding)

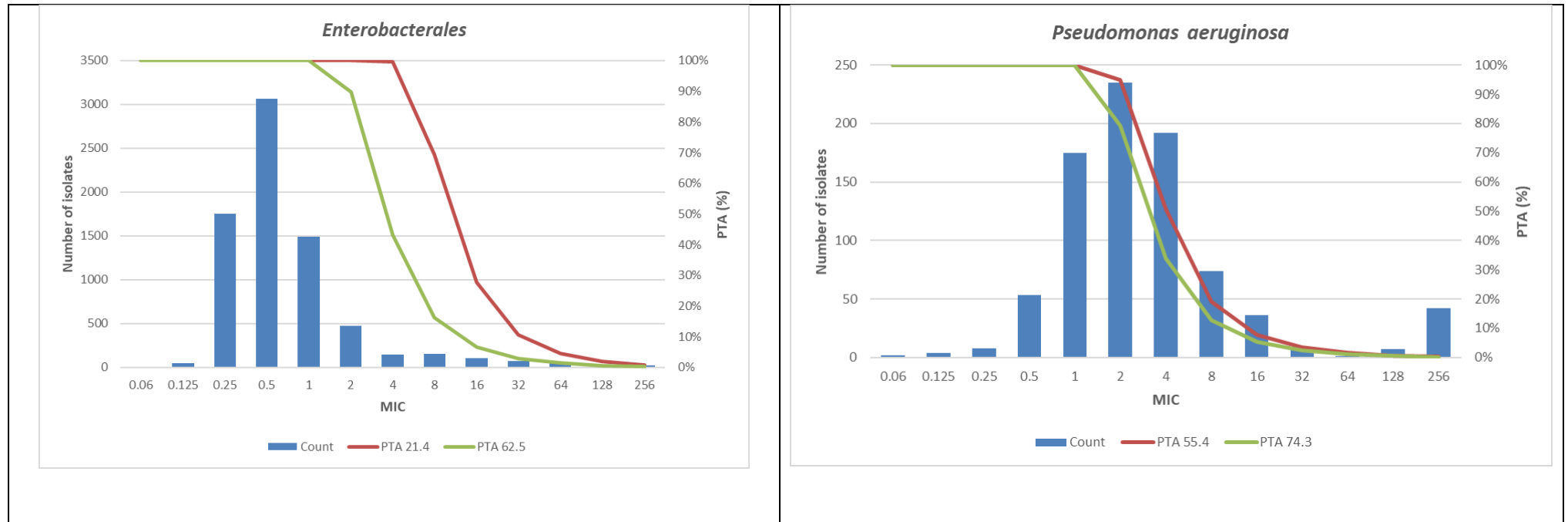
Pharmacodynamics

Index*	Neutropenic mouse thigh*		Neutropenic mouse thigh*		Neutropenic mouse thigh*	
	<i>Enterobacteriales</i>		<i>Pseudomonas aeruginosa</i>		<i>Staphylococcus aureus</i>	
	Median (Range) ^a	Mean ± SD	Median (Range) ^a	Mean ± SD	Median (Range) ^a	Mean ± SD
fAUC/MIC for bacteriostasis	21.4		55.4		41.4	
fAUC/MIC for 1-log ₁₀ kill	62.5		74.3		90.4	

* Data from the combined analysis of amikacin, gentamicin and tobramycin, extrapolated to netilmicin

Monte Carlo simulations

Pharmacokinetic parameters obtained from pooled PK studies: Total body clearance: 2.095 ± 1.447 L/h, Protein binding: <3%. Dosage: 500 mg (~7mg/kg) x 1 iv.



The targets are as described above. For example: PTA 21.4: probability of target attainment for the bacteriostasis target for *Enterobacterales* of fAUC/MIC-21.4 mg.h/L.

Clinical studies

Aminoglycosides are not often used as monotherapy in modern clinical practice (Craig, 2011; Hanberger, 2013). Most often they are used in combination with beta-lactams or other cell wall active agents, as initial empirical therapy for serious infections (e.g. in neonatal sepsis), including sepsis of urinary or abdominal source, complicated urinary tract infection, febrile neutropenia, intra-abdominal infection (e.g. in combinations such as ampicillin or amoxicillin+gentamicin+metronidazole) and hospital-acquired pneumonia. They are also used in combination for the treatment of acute exacerbations of cystic fibrosis (IV or inhaled), as directed therapy against a range of other *P. aeruginosa* infections and in some forms of endocarditis (streptococcal, enterococcal).

The PK-PD analyses presented here essentially apply to the use of aminoglycosides as monotherapy. A 2007 systematic review and meta-analysis of aminoglycoside monotherapy concluded that “the present data support the use of aminoglycosides for urinary tract infections”. The paucity of trials including patients with sepsis or reporting on mortality precludes firm recommendations for patients with infections other than of the urinary tract” (Vidal et al., 2007). The presence of sepsis associated

with urinary tract infection did not adversely affect aminoglycoside outcomes when examined specifically in the meta-analysis. Dosage regimens were not formally examined in this review, a EUCAST review of the references for urinary tract infection particularly complicated UTI (cUTI) showed satisfactory clinical responses to doses of ~3 mg/kg/day for gentamicin and tobramycin; studies on amikacin were too limited to reach a conclusion about dosing for cUTI. EUCAST breakpoints are based on a standard dosing regimen of 25-30 mg/kg/day.

Importantly, aminoglycoside monotherapy will occur in combination regimens when resistance is present to the other agent. For some common aminoglycoside combinations, resistance to the beta-lactam agent is common, e.g. ampicillin/amoxicillin. It is possible that the combination of an aminoglycoside with an agent to which the pathogen is resistant may still have useful clinical activity, although this has never been studied formally. Such combinations should therefore be used with caution in infections outside the urinary tract.

In the context of combination therapy, the relevance of the standard EUCAST approach to the application of target attainment rates (of at least 95%) to infections other than those in or taking origin from the urinary is uncertain. If synergy occurs with combination regimens, it is possible that a lower pharmacodynamic target applies, but there are no studies available that explore this possibility.

Clinical breakpoints

The clinical breakpoints for netilmicin can be found in the most recent version of the Breakpoint tables: https://www.eucast.org/clinical_breakpoints
Breakpoints will appear in brackets when the PK/PD target attainment is suboptimal, but efficacy is expected if the agent is used in combination with other active therapy

References

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