Gentamicin: Rationale for EUCAST Clinical Breakpoints

Current version	**3.0**	**September 2023**
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Introduction

Gentamicin 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, and tobramycin 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 has the lowest activity against this species. The low activity of gentamicin precludes setting breakpoints for this species. Amikacin is active against some organisms with resistance to the other agents, due to its stability to many aminoglycoside modifying enzymes.

Gentamicin 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 and tobramycin, a daily dose of 7-7.5 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 from version 2.0 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		Efficacy studies*	
Dosage			**5-7 mg/kg**	
C_{max} (mg/L)			21.66 (14.40-27.42)[a]	
C_{min} (mg/L)			0.63 (0-3.58) [a]	
Total body clearance (L/h)			4.32 ± 1.28	
T ½ (h), mean (range)				
AUC_{0-12} (mg.h/L)				
AUC_{0-24} (mg.h/L)			91.09 (29.41-217.73) [a]	
$AUC_{0-\infty}$ (mg.h/L)				
Fraction unbound (%)			70-100	
Volume of $distribution_{ss}$ (L)			0.28 ± 0.02	

* Ambrose et al. USCAST Aminoglycoside in vitro susceptibility test interpretive criteria evaluations, v1.3 Feb 2019 (http://www.uscast.org/documents.html)
[a] Median(range) values on days 1-2 for simulated patients with 5-7 mg/kg q24h gentamicin (extended interval) and CLcr 90-120ml/min based on the population PK parmeters Vc=0.28 x Total Body Weight and CL=0.047 x CLcr)

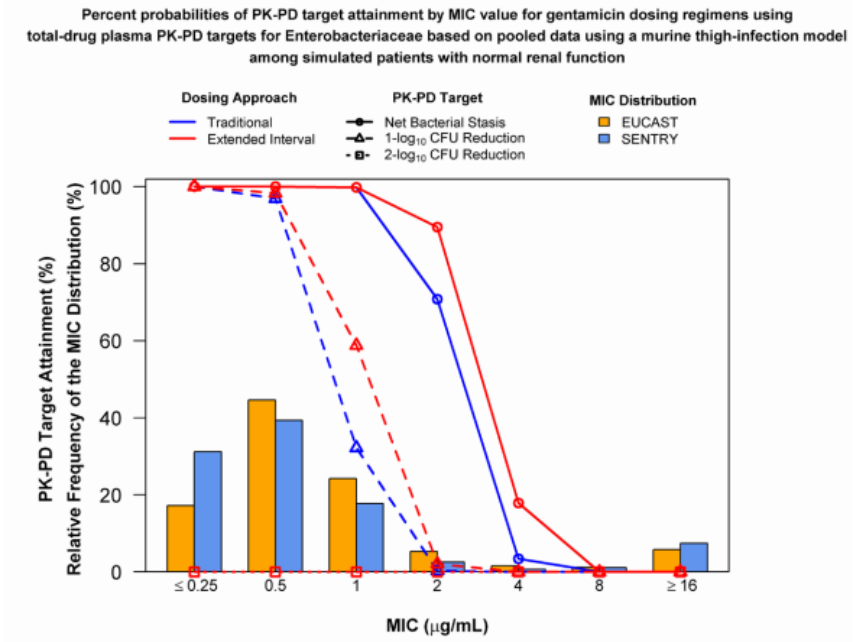
Pharmacodynamics

Index8	Neutropenic mouse thigh*		Neutropenic mouse thigh*		Neutropenic mouse thigh*	
	Enterobacterales		***Pseudomonas aeruginosa***		***Staphylococcus aureus***	
	Median (Range)[a]	**Mean ± SD**	**Median (Range) [a]**	**Mean ± SD**	**Median (Range) [a]**	**Mean ± SD**
*f*AUC/MIC for bacteriostasis	21.4		55.4		41.4	
*f*AUC/MIC for 1-log_{10} kill	62.5		74.3		90.4	

* Ambrose et al. USCAST Aminoglycoside in vitro susceptibility test interpretive criteria evaluations, v1.3 Feb 2019 (http://www.uscast.org/documents.html)
[a] Median values from murine thigh infection model. CV of EC_{50} was <20%

Monte Carlo simulations*

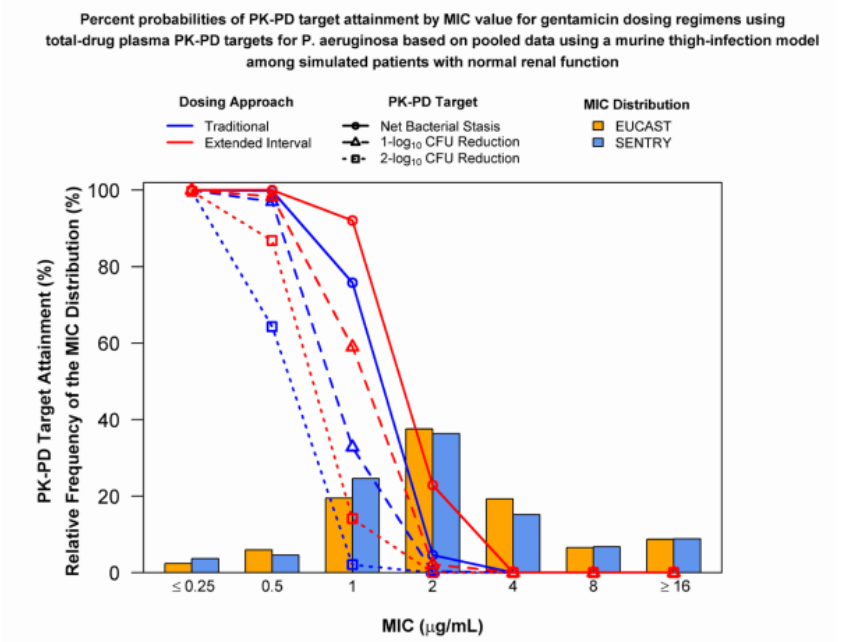
Enterobacterales



MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC[a]			
	Traditional		Extended interval	
	Net bacterial stasis (30.7)	1-log_{10} CFU reduction from baseline (84.3)	Net bacterial stasis (30.7)	1-log_{10} CFU reduction from baseline (84.3)
0.5	100	96.9	100	98.3
1	99.8	32.2	99.8	58.8
2	70.8	0.30	89.5	2.10

a. Percent probabilities of PK-PD target attainment by MIC are shown for each bacterial reduction endpoint. The associated magnitude of the non-clinical total-drug plasma AUC:MIC ratio target for each endpoint based on a Hill model developed using pooled data from a neutropenic murine-thigh infection model is shown in parenthesis in each column header.

Pseudomonas aeruginosa



MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC[a]			
	Traditional		Extended interval	
	Net bacterial stasis (58.3)	1-log_{10} CFU reduction from baseline (83.9)	Net bacterial stasis (58.3)	1-log_{10} CFU reduction from baseline (83.9)
0.5	99.8	97.0	100	98.3
1	75.8	32.8	92.1	59.0
2	4.60	0.30	22.9	2.20

a. Percent probabilities of PK-PD target attainment by MIC are shown for each bacterial reduction endpoint. The associated magnitude of the non-clinical total-drug plasma AUC:MIC ratio target for each endpoint based on a neutropenic murine-thigh infection model is shown in parenthesis in each column header.

* Traditional dosing 80mg x 3; extended interval dosage 240mg x 1

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 for 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 gentamicin 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

- Craig WA. Optimizing aminoglycoside use. Crit Care Clin. 2011;27(1):107-21.
- Hanberger H, Edlund C, Furebring M, Giske CG, Melhus A, Nilsson LE, Petersson J, Sjölin J, Ternhag A, Werner M, Eliasson E; Swedish Reference Group for Antibiotics. Rational use of aminoglycosides--review and recommendations by the Swedish Reference Group for Antibiotics (SRGA). Scand J Infect Dis. 2013;45(3):161-75.
- Vidal L, Gafter-Gvili A, Borok S, Fraser A, Leibovici L, Paul M. Efficacy and safety of aminoglycoside monotherapy: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2007;60(2):247-57.