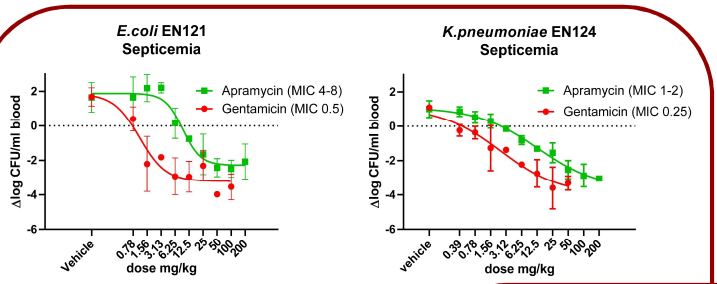
In-vivo Efficacy of Apramycin Against Enterobacteriaceae and *A. baumannii*

STATENS SERUM INSTITUT

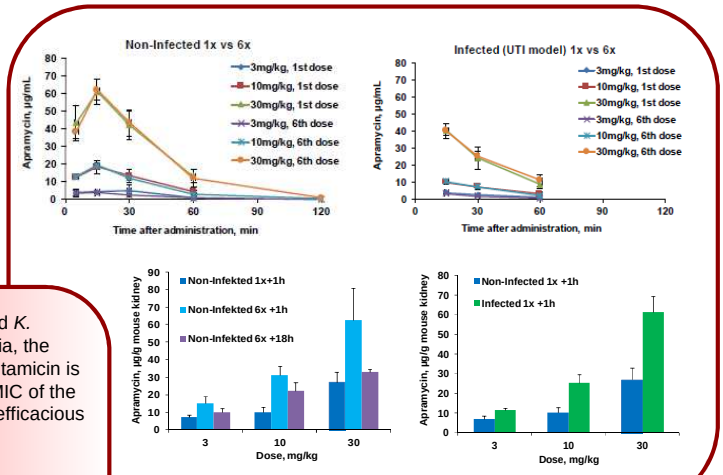
Jon U. Hansen[1], Edgars Liepins[2], Solveiga Grinberga[2], Sven N. Hobbie[3], Carina V. Lundberg[1]
[1] Statens Serum Institut Copenhagen, Denmark. [2] Latvian Institute of Organic Synthesis, Riga, Latvia. [3] Institute of Medical Microbiology, University of Zurich, Switzerland

Aim: Apramycin is an aminoglycoside described to have a broad activity against multidrug resistant Enterobacteriaceae and *A. baumannii.* In this study, we evaluate the efficacy of apramycin in murine infection models with *E. coli, K. pneumoniae* and *A.baumannii*.

Conclusion: Apramycin is efficacious against aminoglycoside resistant clinical isolates that are untreatable with gentamicin in mice. Apramycin is undergoing further preclinical evaluation as a candidate for development into a human therapeutic.

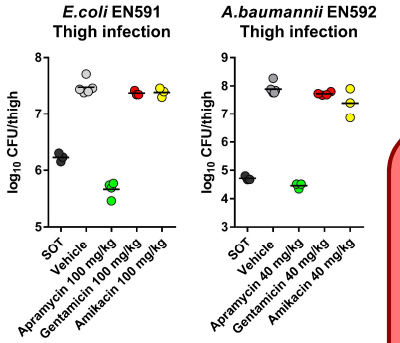


Model	Drug	Efficacy (mg/kg)	*E.coli* EN121	*K.pneu* EN124
Septicemia	APR	ED50	9.2	12.7
		-1 log	13.1	9.4
		-2 log	24.1	29.5
	GEN	ED50	1.1	3.2
		-1 log	1.3	1.4
		-2 log	2.1	4.8
Pneumonia	APR	ED50	-	26
		-1 log	-	18.5
		-2 log	-	56



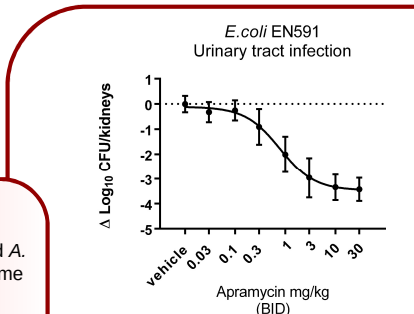
Left: Against *E.coli* EN121 and *K. pneumoniae* EN124 septicemia, the efficacy of apramycin and gentamicin is comparable and reflects the MIC of the two drugs. Apramycin is also efficacious against EN124 pneumonia.

Right: Apramycin is excreted unmodified in urine (data not shown) and in healthy mice, repeated dosing (BID, three days) leads to an accumulation in kidney tissue, but does not influence plasma levels. In urinary tract infected mice, plasma AUC was reduced approx. 20% and kidney accumulation was increased approx 2.5-fold



Left: In thigh-infected mice, a single dose of apramycin is efficacious against aminoglycoside-resistant *E. coli* EN591 and *A. baumannii* EN592 whereas gentamicin and amikacin at the same dose does not reduce the bacterial load.

Right: In urinary tract infection, a low dose of apramycin given BID for two days significantly reduce the bacterial burden of aminoglycoside resistant *E.coli* EN591 in urine, bladder and kidney.



Efficacy	Kidney (mg/kg)	Bladder (mg/kg)	Urine (mg/kg)
ED50	0.84	0.28	0.99
-1 log	0.27	0.02	0.04
-2 log	0.95	0.12	0.36
-3 log	3.87	1.53	1.73

Methods: A single dose apramycin was initially evaluated in a septicemia model in female NMRI mice and in a pneumonia model in female DBA/2 mice. Mice were inoculated with aminoglycoside-susceptible clinical isolates *E.coli* EN121 or *K. pneumoniae* EN124. Next we established mouse models of thigh infection in female NMRI mice and cUTI in female C3H/HeJ mice using gentamicin-resistant *E. coli* EN591 and *A. baumannii* EN592. Mice were treated subcutaneously with a single dose (thigh model) or BID for two days (UTI model), vehicle or control antibiotics and bacterial loads in relevant compartments were quantified before and after treatment. Apramycin pharmacokinetics and elimination was evaluated in healthy and infected mice.

MICs (mg/L) of in-vivo isolates used

Species	ID	RMT	APR	GEN	AMK
E.coli	EN121	-	4-8	0.5-1	2
K.pneumoniae	EN124	-	1-2	0.25	1
A.baumannii	EN592	*armA*	4	>256	>256
E.coli	EN591	*rmtB*	4-8	>256	>256

References
Juhas, M. et al (2019). J Antimicrob Chemother **74**(4): 944-952

Contact: JOA@SSI.dk
CVL@SSI.dk

The research leading to these results has received support from the Innovative Medicine Initiative Joint Undertaking under grant agreement no 115583, resources of which are composed of financial contributions from the European Union`s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies` in kind contribution.

efpia imi innovative medicines initiative ND4BB ENABLE