Balancing efficacy and reduction in renal function to optimize gentamicin dosing in children with cancer

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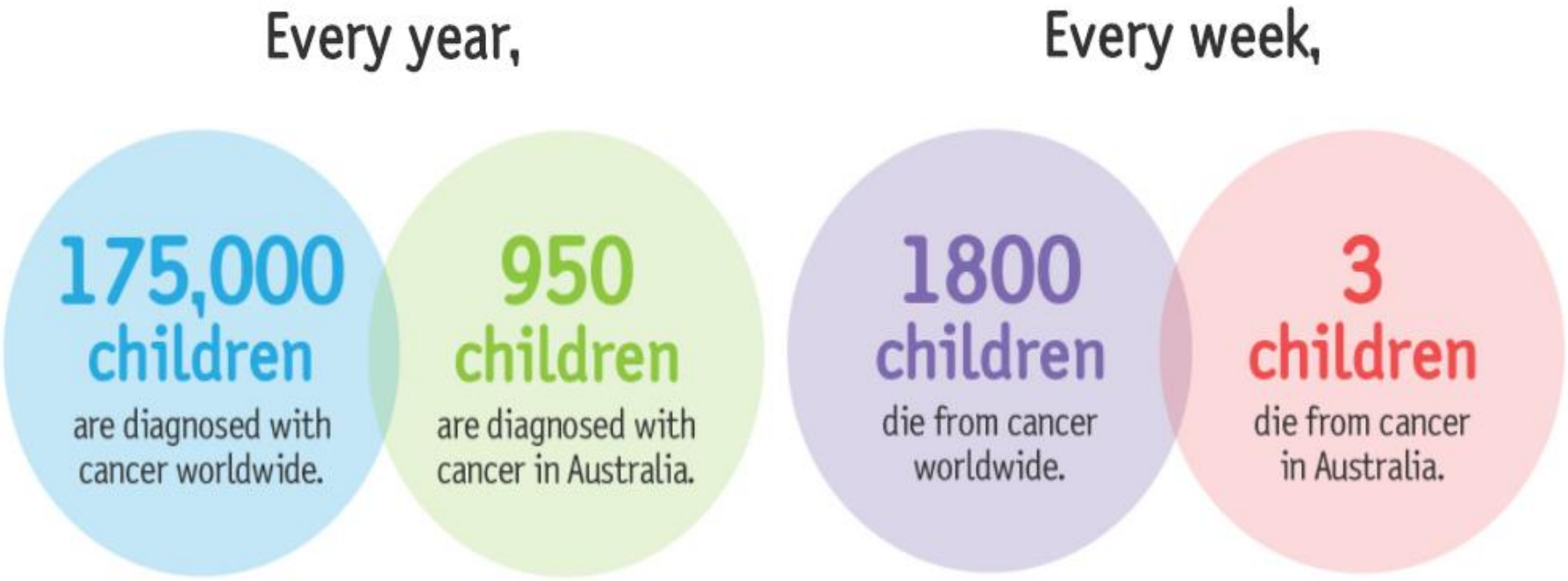
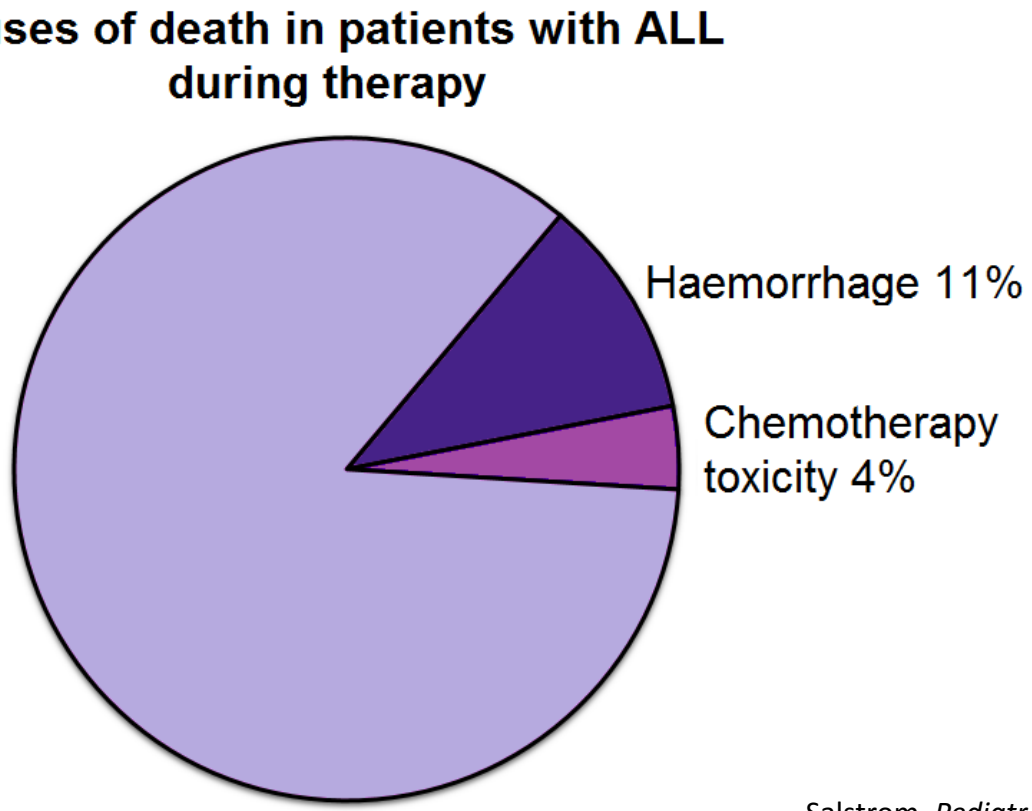
Childhood cancer



http://www.aihw.gov.au/child-health/health/#mortality
https://www.stbaldricks.orgAIHW

Childhood cancer and gentamicin



Salstrom. *Pediatr Blood Cancer* 2015
Asim. *JPMA* 2011

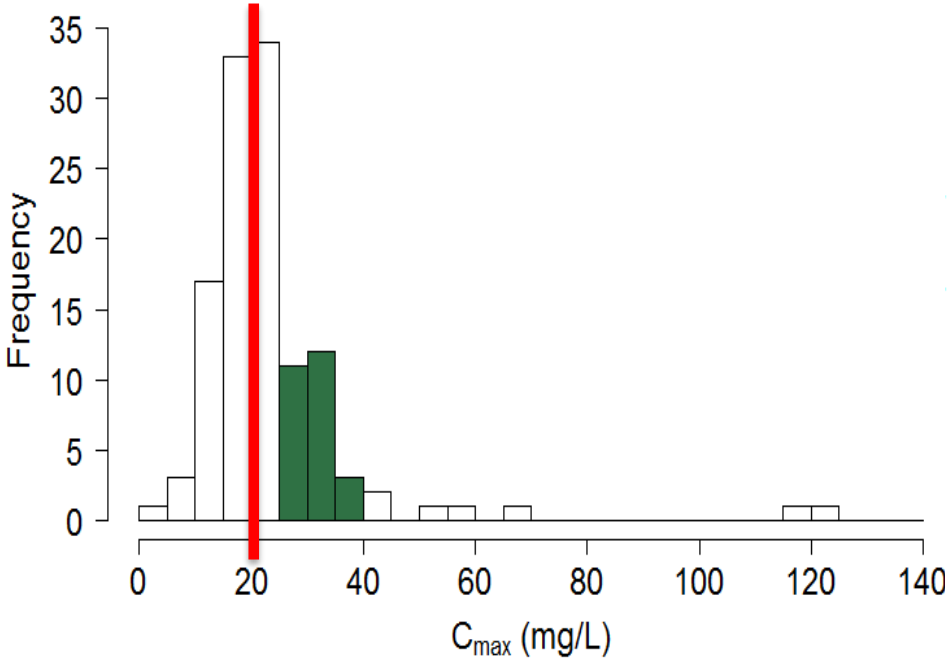
Current dosing and clinical exposure targets for gentamicin

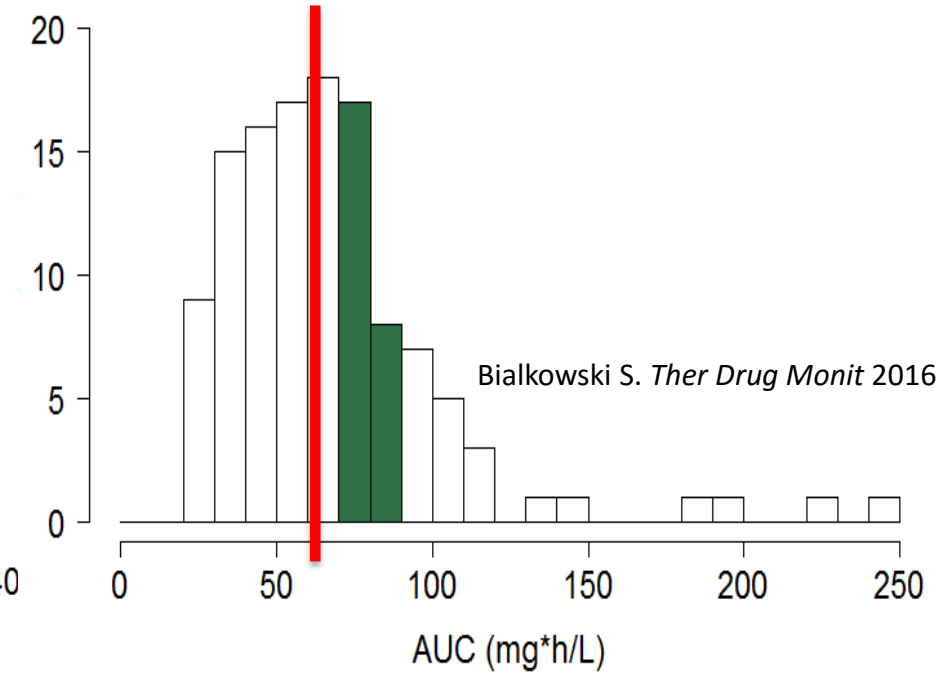
- Current initial dose recommendation:
  - Patients < 10 years: 7.5 mg/kg/24 hours
  - Patients ≥ 10 years: 6 mg/kg/24 hours

- Current exposure institution guideline targets:
  - C_{max} of 25 – 40 mg/L
  - AUC_{24} of 70 – 90 mg*h/L

Difficulties in dosing gentamicin in paediatric oncology patients

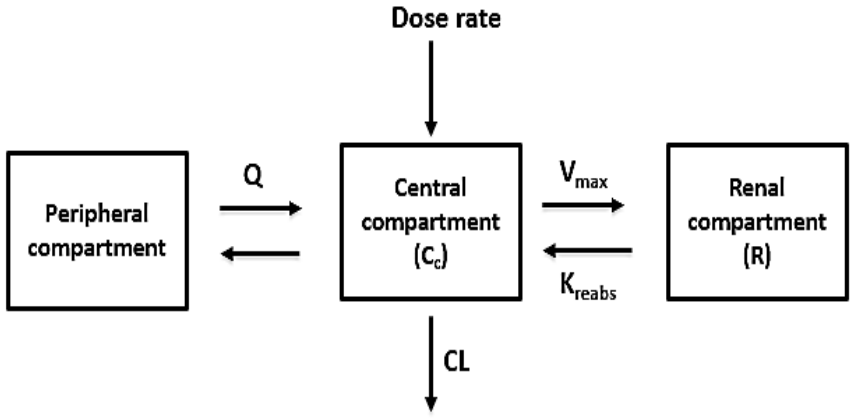
54% of patients do not achieve exposure targets, even after several dose adjustment

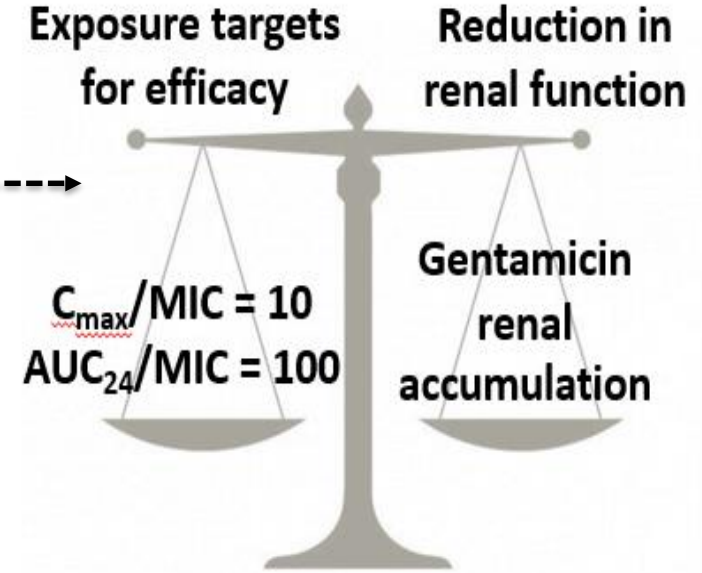




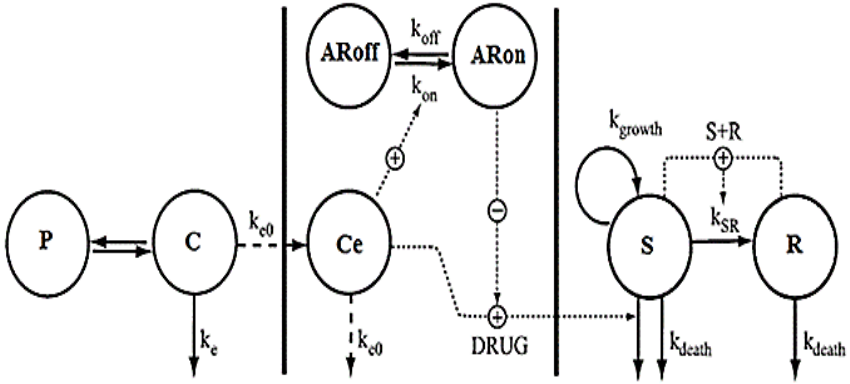
Bialkowski S. *Ther Drug Monit* 2016

Population PK model and renal compartment





Semi-mechanistic PD model to explore bacterial killing over time



Initial dose

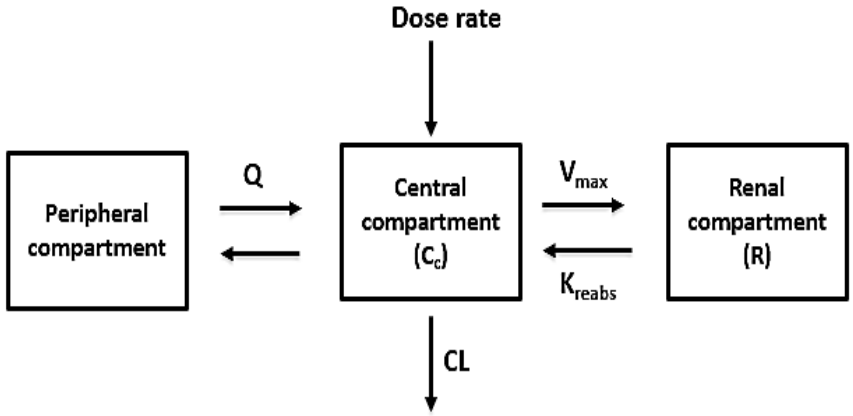
Patient demographics

Patient characteristics	Values (n=475) Mean (95% CI)
Total body weight (kg)	25.6 (24.0 – 27.3)
Fat-free mass (kg)	19.4 (18.3 – 20.5)
Post-natal age (years)	6.47 (6.38 – 6.56)
Post-menstrual age (weeks)	376.4 (355.2 – 397.6)
GFR_{mat} (mL/min)	40.8 (39.1 – 42.6)

GFR_{mat}: maturation of glomerular filtration rate calculated using equation developed by Rhodin et al.

Rhodin *Pediatr nephrol* 2009

Population PK model and renal compartment



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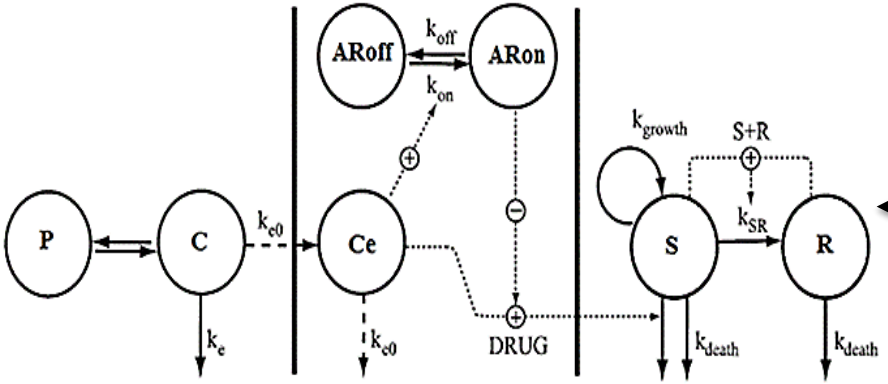
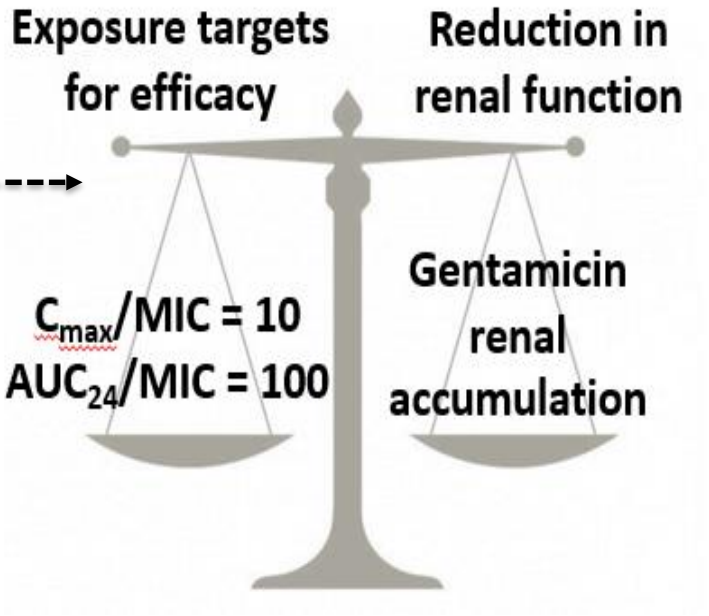




Initial dose

icacy targets were equally weighted

Exposure targets for efficacy

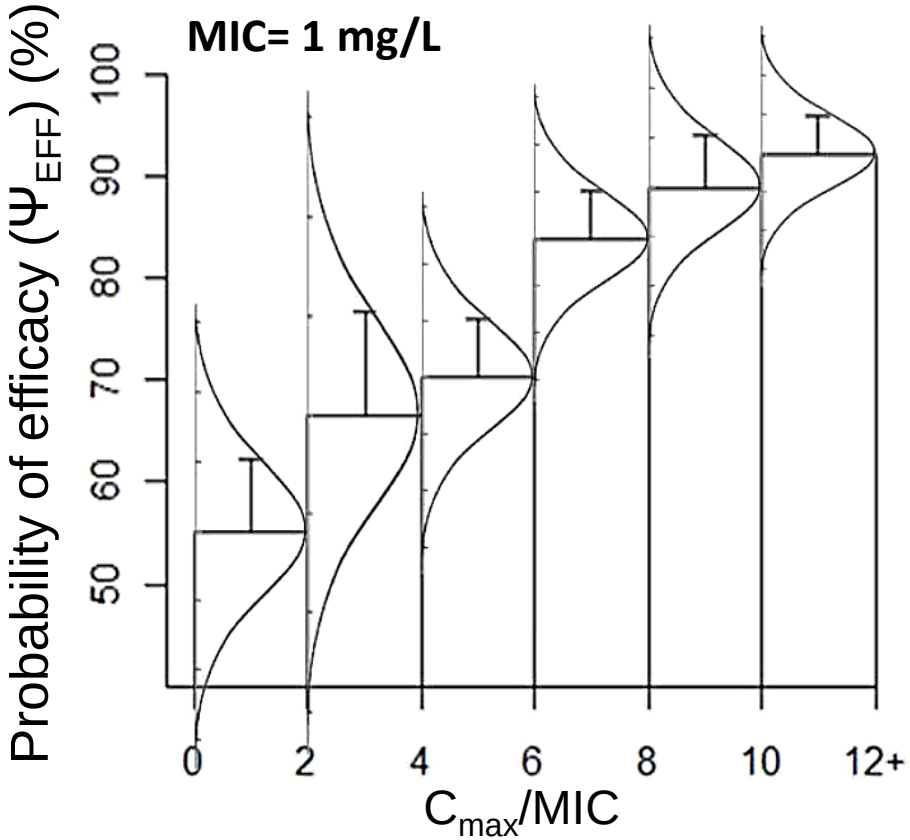


Figure from Moore et al. and adapted by Standing et al.

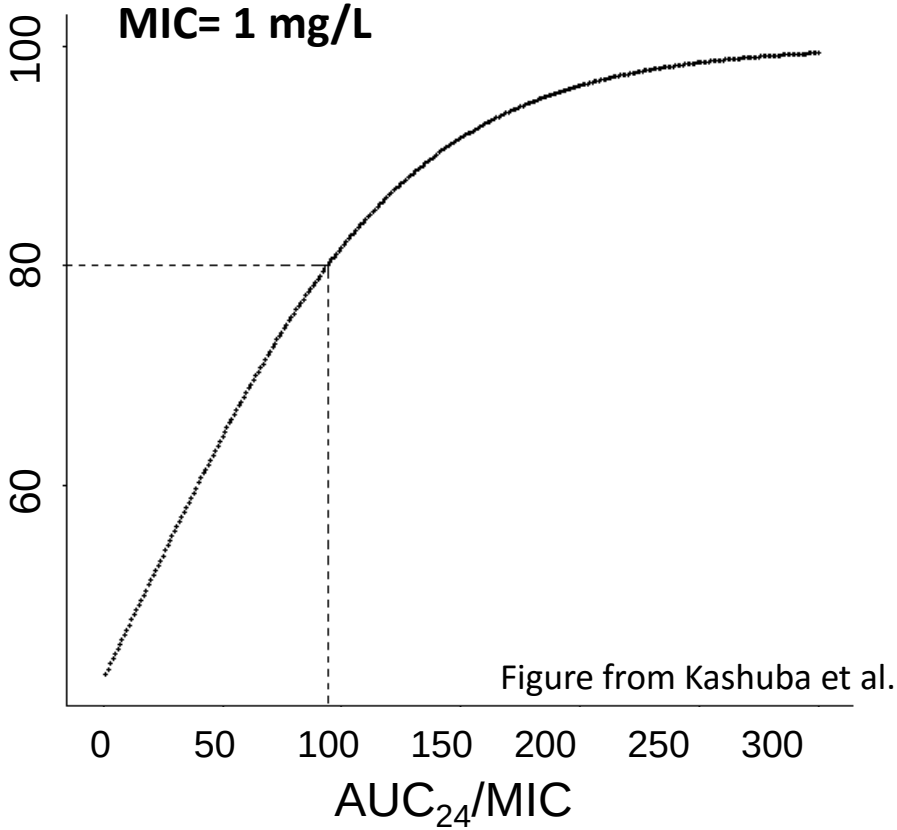
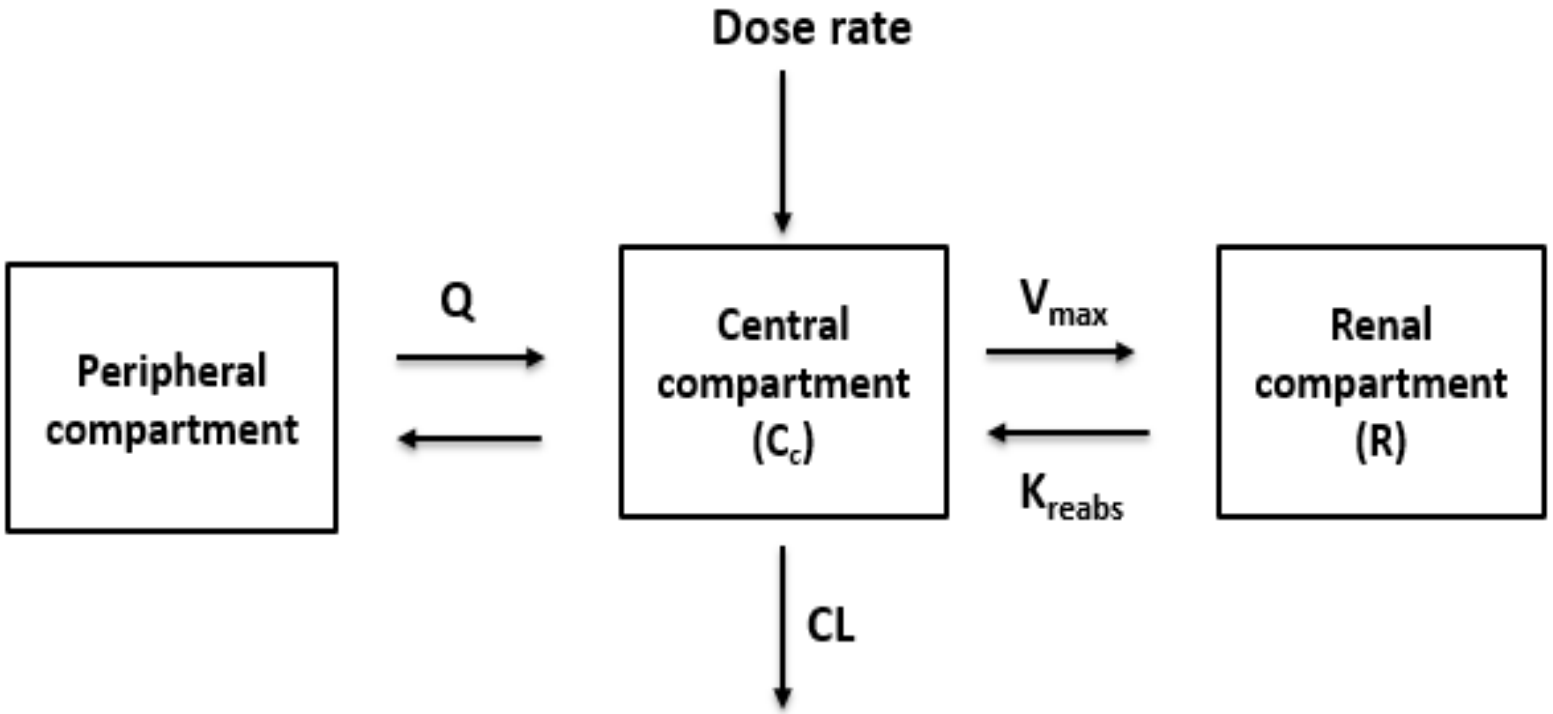


Figure from Kashuba et al.

Standing In *PAGE* meeting Athens 2011
Moore *J infect Dis* 1987
Kashuba *Antimicrob Agents Chemother* 1999

Gentamicin accumulation in the renal cortex



Llanos-Paez *Antimicrob Agents Chemother, 2017*
Rougier *Antimicrob Agents Chemother,* 2003

Gentamicin accumulation in the renal cortex

$$A_R(t) = -K_{reabs} \times A_R + V_{max} \times \frac{C_c}{K_m + C_c}$$

Renal compartment (R)

Llanos-Paez *Antimicrob Agents Chemother, 2017*
Rougier *Antimicrob Agents Chemother,* 2003

Effect of gentamicin renal accumulation

$$A_R(t) = -K_{reabs} \times A_R + V_{max} \times \frac{C_c}{K_m + C_c}$$

Renal compartment (R)

$$\text{If } A_R\,(mg) < 42.5\ mg \quad E_{GFR}(t) = 0$$

$$\text{If } A_R\,(mg) > 42.5\ mg \quad E_{GFR}(t) = E_{max} \times \frac{A_R^{\gamma}}{A_{R50}^{\gamma} + A_R^{\gamma}}$$

Llanos-Paez *Antimicrob Agents Chemother, 2017*
Rougier *Antimicrob Agents Chemother,* 2003

Reduction in renal function

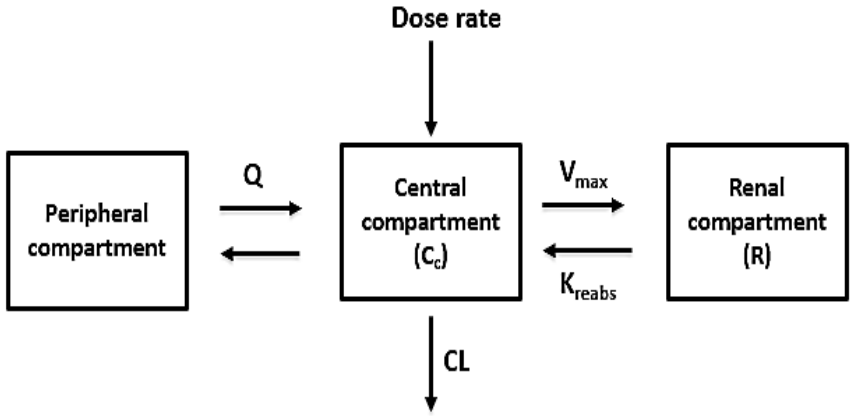
$$GFR_{new}(mL/min) = GFR_0 - (GFR_{max} \times \frac{E_{GFR}{}^{\delta}}{E_{GFR50}{}^{\delta} + E_{GFR}{}^{\delta}})$$

Relative reduction in renal function

$$\text{Relative change in GFR } (r\Delta GFR) = \frac{(GFR_0 - GFR_{new})}{GFR_0}$$

Rougier *Antimicrob Agents Chemother,* 2003

Population PK model and renal compartment



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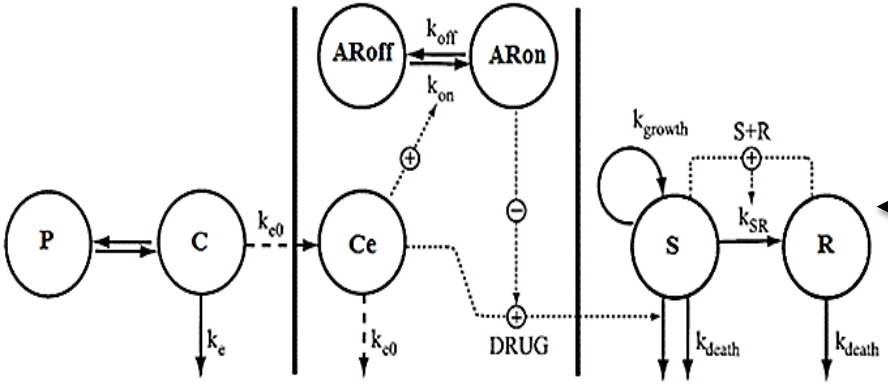
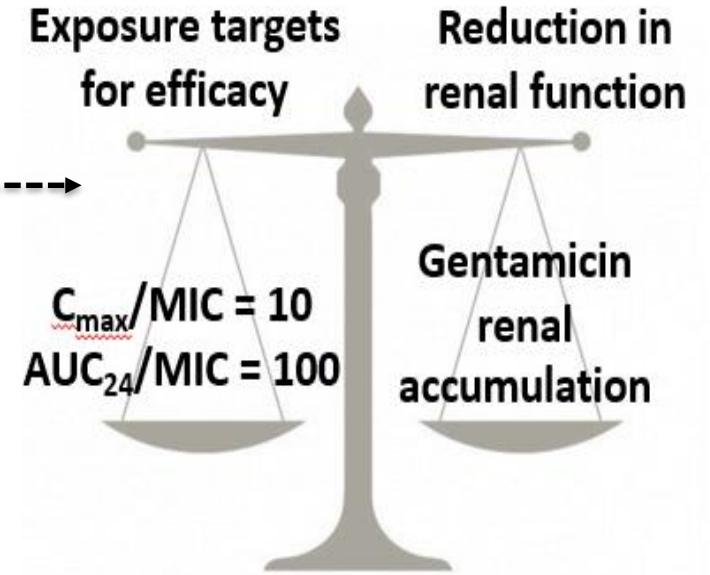




Initial dose

Initial dose

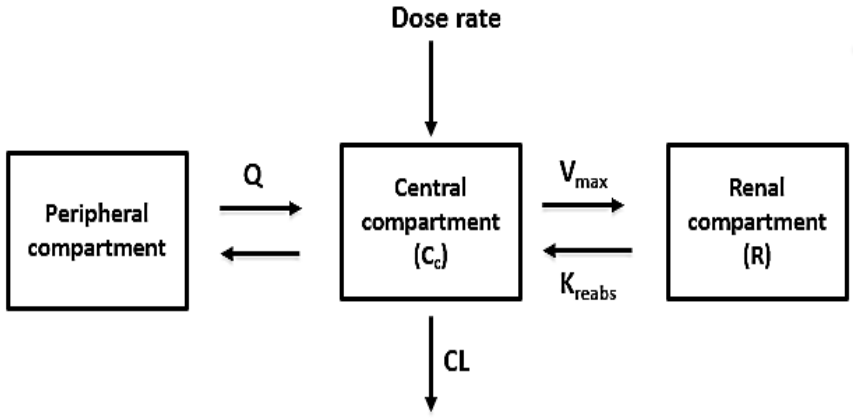
Estimation of an optimal initial gentamicin dose **for different microorganism's MICs** using a logit function in NONMEM®

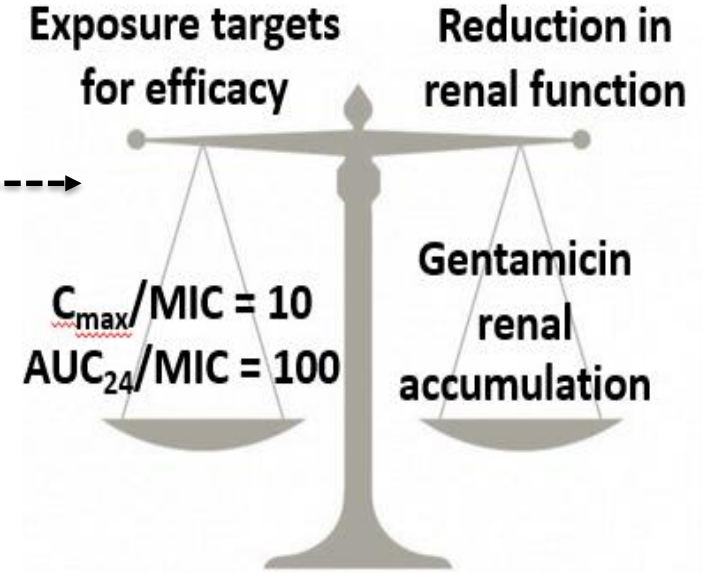
$$\text{logit}(\Psi_{EFF}) = \log(\Psi_{EFF}) - \log(1 - \Psi_{EFF})$$

$$\text{logit}\,(r\Delta GFR) = \log(r\Delta GFR) - \log(1 - r\Delta GFR)$$

$$\mathcal{U}(x, \theta) = \text{logit}(\Psi_{EFF}(x, \theta)) - \text{logit}(r\Delta GFR(x, \theta))$$

Population PK model and renal compartment





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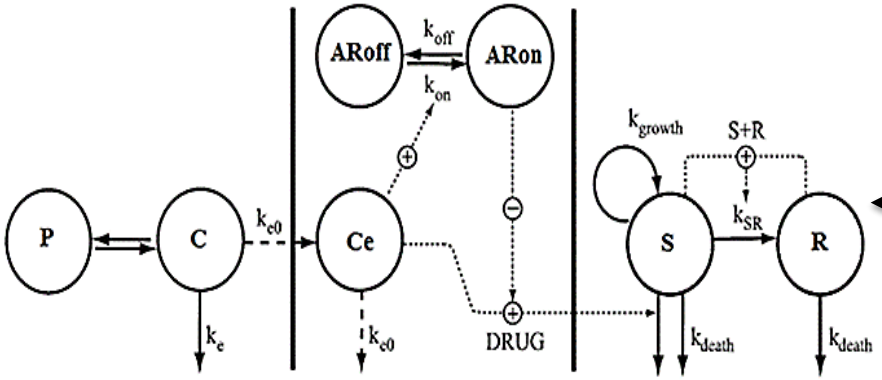
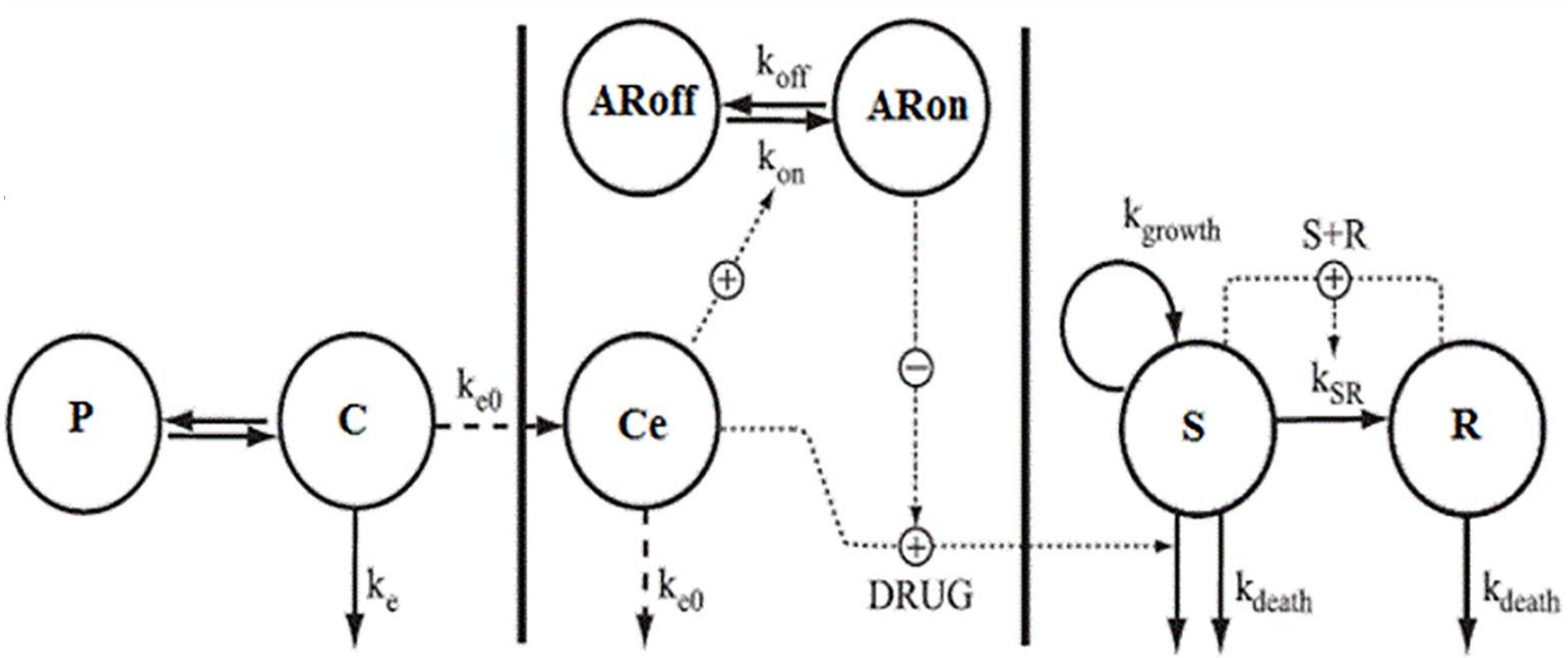


Initial dose

Semi-mechanistic PD model to explore bacterial killing over time



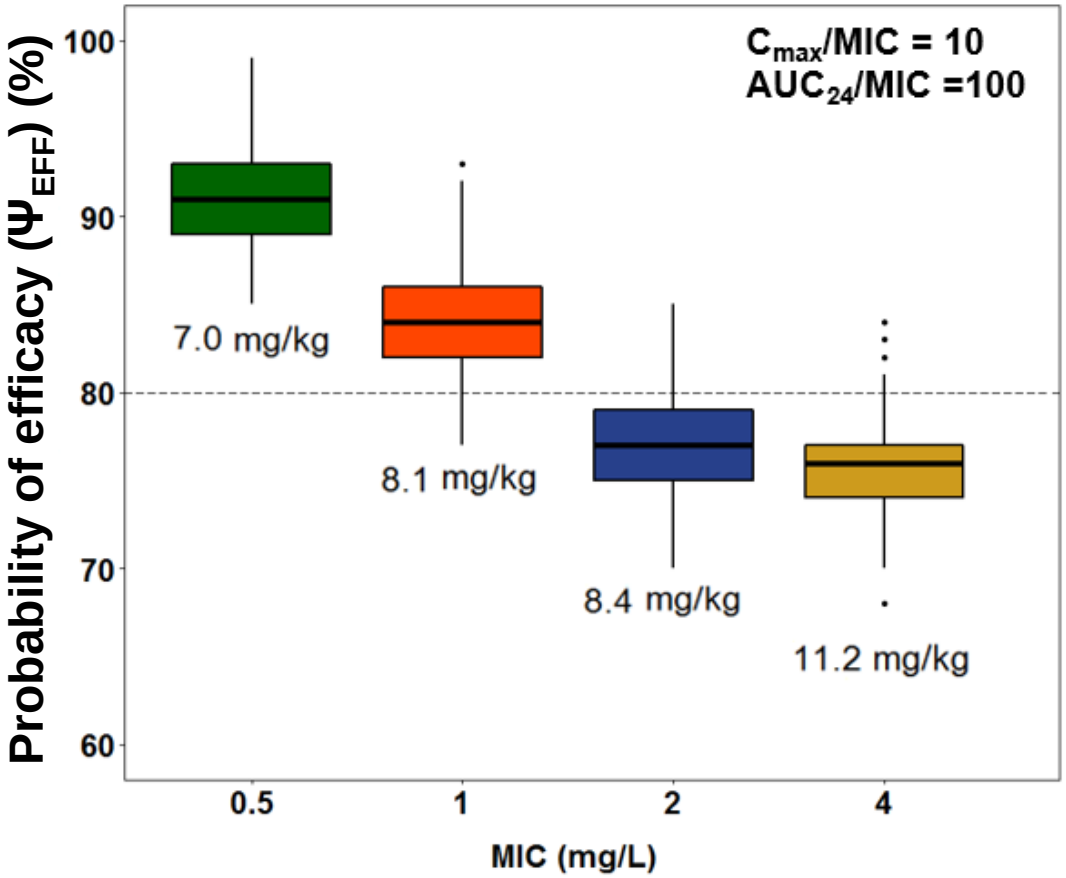
Mohamed *Antimicrob Agents Chemother* 2012

Results

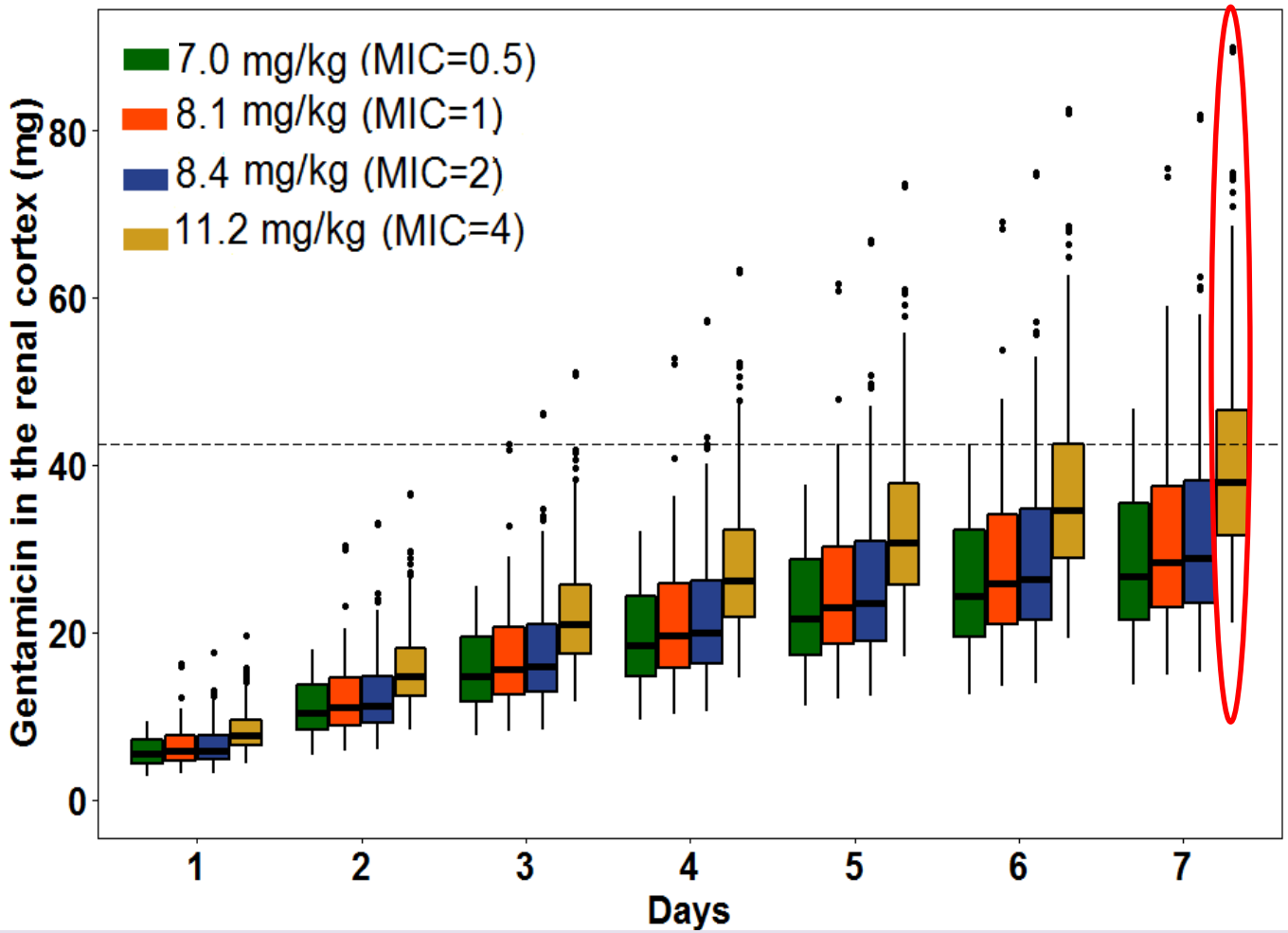
MIC (mg/L)	Dose (mg/kg)	Ψ_{EFF} (%) Mean	rΔGFR (%) Mean
0.5	7.0	91.2	0.3
1	8.1	84.0	0.7
2	8.4	76.8	1.7
4	11.2	75.9	3.8

MIC: minimum inhibitory concentration; Ψ_{EFF}: probability of efficacy; rΔGFR: relative change in renal function

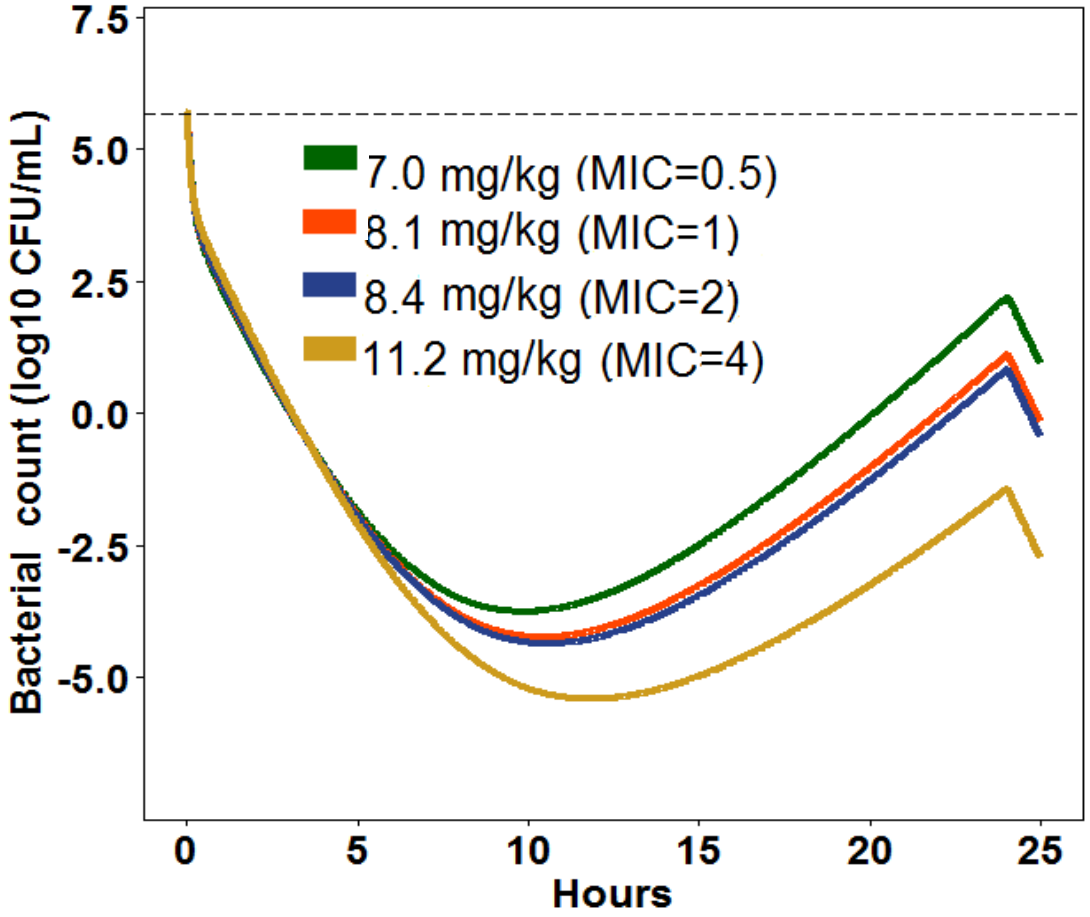
Doses estimated and probability of efficacy



Gentamicin renal accumulation



Simulation from semi-mechanistic PD model



Summary

- An utility function estimated optimal initial dose of gentamicin balancing probability of efficacy and reduction in renal function

- An initial dose of 7.0 mg/kg, commonly administered in clinical practice, may not achieve adequate efficacy for microorganisms with a MIC of > 0.5 mg/L

Acknowledgments

Dr Christine Staatz
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