

Probability of Target Attainment for Gentamicin Dosing in Modeled Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapies

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Abstract 91

Introduction

- The challenge in dosing gentamicin in patients with AKI is the high risk of nephrotoxicity when the mean 24-hour area under the curve (AUC₂₄) is above 120 mg*h/L.^[1]
- Gentamicin efficacy is associated with peak concentration to minimal inhibitory concentration (MIC) ratio of > 10 and an AUC₂₄ between 70-120 mg*h/L.^[1]
- Susceptible organisms have MIC ≤ 4 mg/L^[13]
- PIRRT, a daily prolonged intermittent RRT, is employed to treat critically ill patients with acute kidney injury.
- Monte Carlo simulations can be used to predict the probability of target attainment of gentamicin in various dosing regimens in patients receiving daily PIRRT.

Objective

To evaluate the probability of target attainment at MIC ≤ 1, 2, and 4 mg/L of gentamicin regimens and to determine initial optimal dosing recommendations in critically ill patients receiving PIRRT

Methods

Mathematical PK Model Development

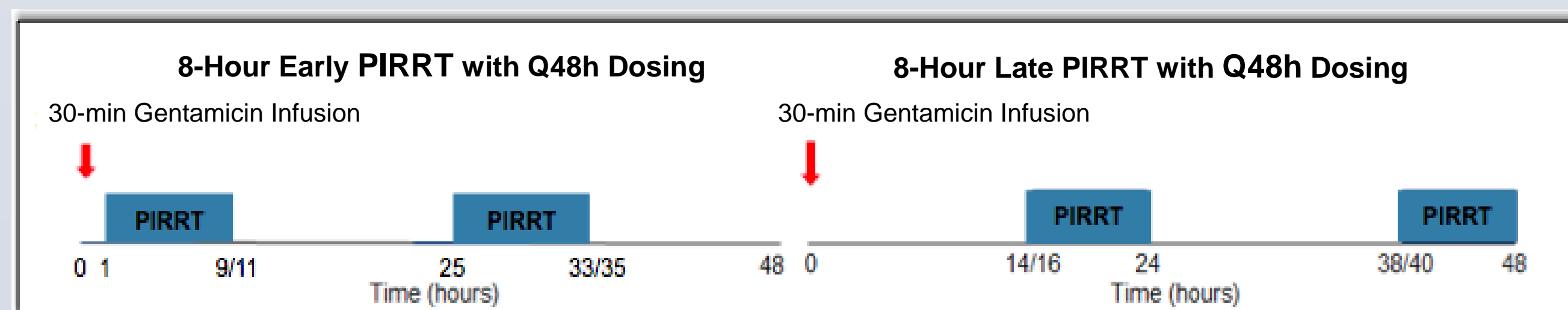
- One compartment pharmacokinetic (PK) model with first order elimination was structured to predict gentamicin disposition for 48 hours of initial therapy.
- V_d, CL_{NR}, and SA averages, standard deviations, and ranges were based on patient data from previous PK studies on gentamicin.

Table 1. Input Parameters Used in In-Silico PK Trials^[1-12]

Gentamicin Parameters		8 Hour PIRRT	10 Hour PIRRT
Q _{blood}		300 mL/min	300 mL/min
Q _{effluent}		83 mL/min	67 mL/min
Frequency		Daily	Daily
Unbound Fraction		0.95	
Mean ± SD [Range]	Volume of Distribution (V _d)	0.374 ± 0.102 L/kg [0.09-1.19 L/kg]	
	Weight	86.6 ± 29.2 kg [40-150 kg]	
	Non-renal Clearance (CL _{NR})	9.2 ± 6.3 mL/min [1.4-34.5 mL/min]	
	Saturation Coefficient (SA)	0.79 ± 0.05 [0-1]	

Monte Carlo Simulation (MCS)

- MCS was performed to generate individual gentamicin concentration profiles in 5,000 virtual patients.
- Gentamicin doses of 6, 8, 10, and 12 mg/kg were simulated based on Q24h and Q48h regimens. Q24h regimens used a maintenance dose of 5 mg/kg.



Prediction of Probability of Target Attainment (PTA)

- The PTA was evaluated by the fraction of virtual patients attaining >90% free gentamicin concentration above 10 times MIC of susceptible organisms during the first 48 hours of therapy; MIC ≤ 1, 2, and 4 mg/L were evaluated.
- The ideal dosing scheme would attain PTA > 90% on day 1, while maintaining mean 24-hour AUC above 70 mg*h/L to ensure efficacy and below 120 mg*h/L to reduce risk of nephrotoxicity.

Results

- 8 and 10 hour PIRRT MCS had similar pharmacokinetic profiles.
- No late PIRRT regimen could attain 90% PTA (efficacy) while also achieving AUC₂₄ < 120 mg*h/L (toxicity).
- On day 1, all dosing schemes met the goal of 90% PTA for MIC ≤ 1mg/L.

Fig 1. Day 1 PTA for 8 Hour HD

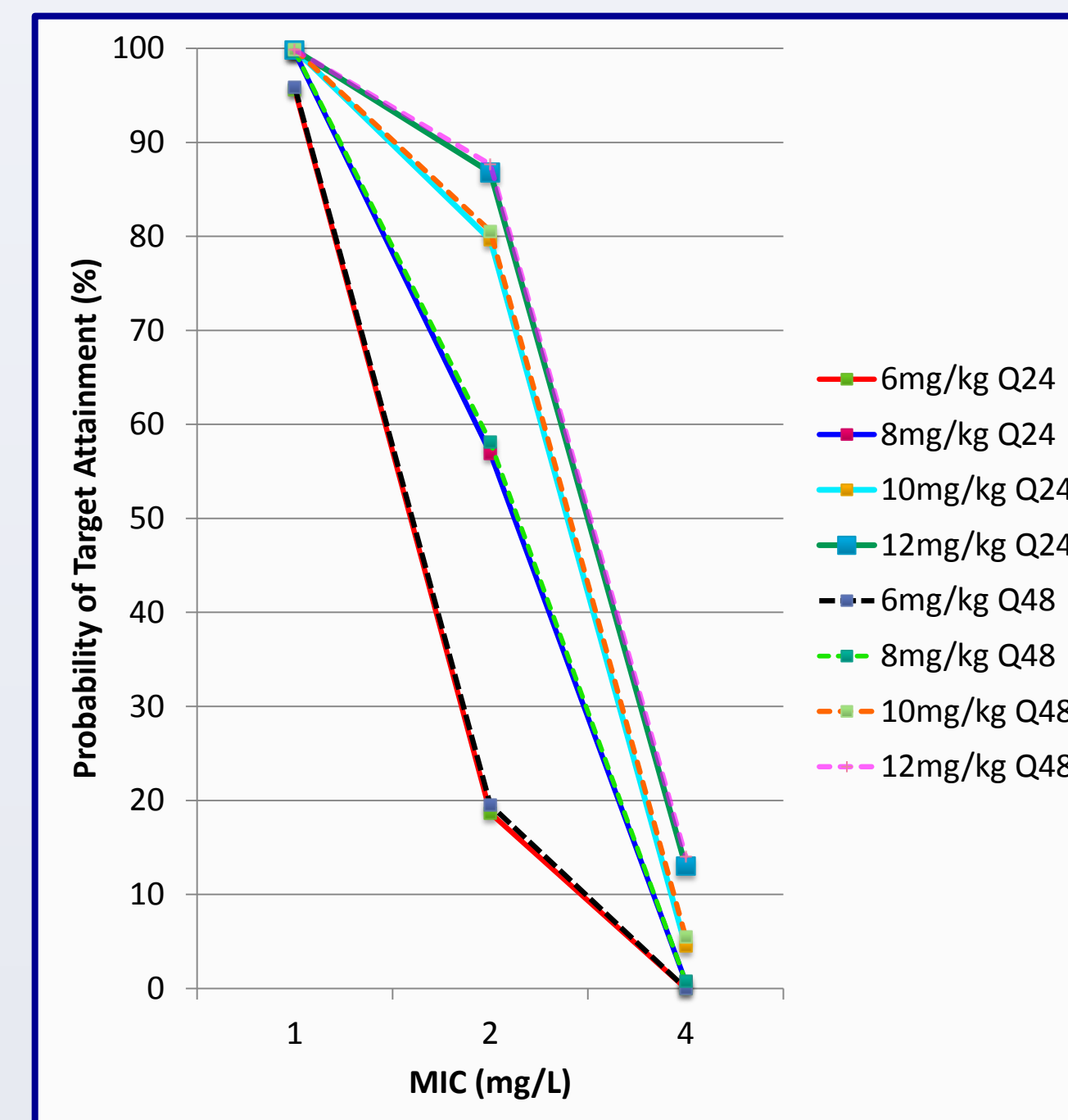


Fig 2. Day 2 PTA for 8 Hour HD

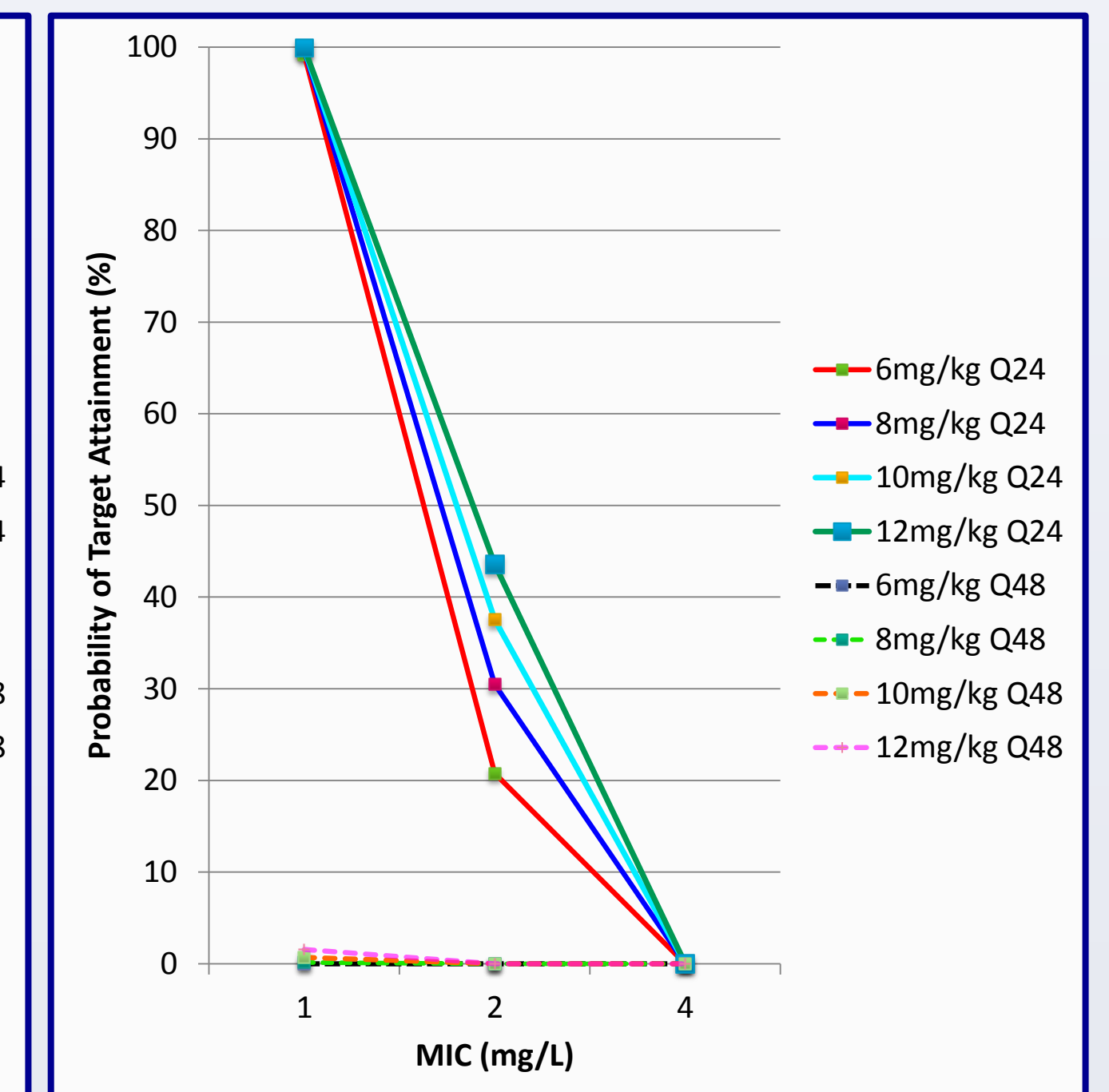


Table 2. Average AUC on Days 1 and 2 in 5000 Virtual Patients Receiving Early PIRRT Gentamicin Regimens with 1g Maximum Dose

Dose at Time 0	Q24h Schedule, Day Two MD 5mg/kg				Q48h Schedule			
	8h PIRRT Average AUC (mg*h/L)		10h PIRRT Average AUC (mg*h/L)		8h PIRRT Average AUC (mg*h/L)		10h PIRRT Average AUC (mg*h/L)	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
6mg/kg	140	158	147	165	140*	41*	147*	43*
8mg/kg	185	171	194	179	184*	53*	195	57
10mg/kg	222	181	234	189	221*	63*	234	67
12mg/kg	247	187	260	194	247	69	261	73

*Bolded numbers illustrate regimens achieving mean AUC₂₄ < 120 mg*h/L
**"Best" regimen for empirical treatment, mean AUC₂₄ = 142

- Only Q24h dosing schemes achieved efficacy targets on day 2.
- Only Q48h dosing schemes were below the toxicity threshold.

Discussion/Conclusion

- No regimen met both efficacy and toxicity targets on both days.
- The "best" regimens of Q48h 8-10mg/kg dosing is based on weighing efficacy benefits and toxicity risks, with a greater focus on efficacy.
- Even the "best" Q48h regimen fell below the efficacy target to a mean AUC₂₄ value of 63 mg*h/L on day 2.
- Roberts JA, et al.^[1] recommended a 6mg/kg Q48h regimen, but they assumed MIC ≤ 1mg/L and prescribed a 10-hour hemodiafiltration with dialysate flow rate of 50mL/min. This is consistent with our findings.
- MCS suggests that it is difficult to reach 90% PTA with gentamicin in critically ill AKI patients receiving PIRRT, but if used, doses should be given an hour before daily PIRRT for highest likelihood of achieving PTA.

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