Monte Carlo Simulations to Determine Optimal Levofloxacin Regimens for *Streptococcus pneumoniae* Infections in Patients Receiving SHIFT Renal Replacement Therapy

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Abstract 72

Introduction

- Levofloxacin is extensively used as empirical and directed therapy for infections in critically ill patients due to its activity against common Gram positive pathogens including *Streptococcus pneumoniae* and many Gram negative organisms.[1]
- A levofloxacin dose of 500 mg q 48 hours has been recommended for patients receiving continuous RRT [2], however levofloxacin pharmacokinetic (PK) data in SHIFT do not exist.
- SHIFT is a daily 8-10 hour renal replacement therapy (RRT) for treating acute kidney injury in critically ill patients.
- Current antibiotic dosing regimens often result in subtherapeutic concentrations in critically ill patients. [3]
- Monte Carlo Simulation (MCS) was used to determine optimal antibiotic doses in patients with other RRT modalities except SHIFT RRT. [4]
- Precise levofloxacin dosing is important because at higher levofloxacin doses cardio- and neurotoxicity have been reported and dosage reduction in renal disease patients is recommended.[5,6]
- Proper dosing recommendations of levofloxacin for S. *pneumoniae* infections in critically ill patients receiving SHIFT RRT is needed.

Objective

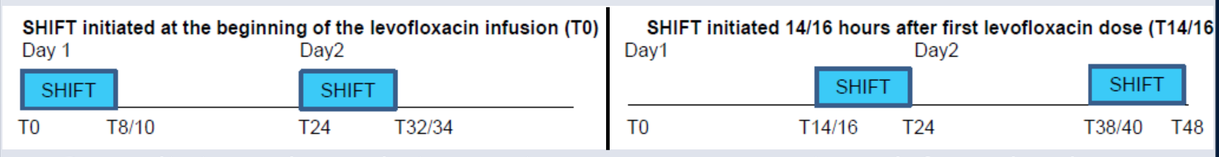
To use Monte Carlo Simulation to determine appropriate levofloxacin doses for *Streptococcus pneumoniae* infections in critically ill patients with SHIFT RRT.

Methods

Mathematical PK Model Development

- Demographic and PK parameters and associated variability from previously published levofloxacin studies in critically ill patients were collated to develop models for virtual patients receiving four common daily SHIFT RRT. [Table 1]
- A one compartment PK model with first order elimination and daily 8- or 10-hour SHIFT RRT was created to predict levofloxacin deposition for 72 hours of initial therapy.
- Four different SHIFT RRT regimens were modelled to be instituted either at the beginning of (early SHIFT) or 14-16 hours after levofloxacin administration (late SHIFT) to ensure a broad range of clinical scenarios and to assess the effect of time of SHIFT in relation to levofloxacin dose. [Figure 1]

Figure 1. Daily SHIFT RRT Settings Occurring at 2 Different Times Relative to Levofloxacin Dose



- Range limits and correlation on input parameters estimated from the data were included in the models to construct a virtual cohort with population-specific pharmacokinetic parameters.

Table 1. Input Parameters Used in Monte Carlo Simulation Trials [1, 7-8]

		Hemofiltration (HF)		Hemodialysis (HD)	
SHIFT Settings	$Q_{effluent}$	5L/h	4L/h	5L/h	4L/h
	Q_{blood}	300 mL/min			
	Duration	8 hours	10 hours	8 hours	10 hours
	Frequency	Daily			
PK Parameters Mean±SD (range limits)	Weight (kg)	86.6 ± 29.2 (40,∞)			
	V_d (L/kg)	1.2±0.4 (0.7,2.08)			
	CL_{NR} (mL/min)	25.7±14 (0.12,67)			
	SC or SA	0.6±0.2 (0,1)			

Monte Carlo Simulation

- The 8 recommended dosing regimens with conventional or loading dose with post-SHIFT dosing, as defined in Table 2, were simulated.
- MCS was performed to generate drug concentration profiles for each regimen in a different group of 5,000 virtual patients.

Prediction of Probability of Target Attainment (PTA)

- The PTA was evaluated by the average daily area under the total serum levofloxacin concentration time curve (AUC_{24h}) of ≥ 50 to the minimum inhibitory concentration (MIC) of 2 mg/L (MIC for sensitive *Streptococcus pneumoniae*) for the first 72 hours of therapy. [9-11]
- The optimal regimen was defined as occurring when ≥ 90% of 5,000 virtual patients reached the PTA target with the lowest daily doses to minimize the risk of toxicity.

Results

- All simulated SHIFT modalities and settings displayed similar results.
- Levofloxacin administered as a loading dose of 750 mg with 500 mg q 24 hours post-SHIFT yielded a PTA ≥ 90% in all 8 SHIFT settings. (Figure 2 shows the PTA results of 10-hour late SHIFT hemodialysis as a representative modality)
- Most recommended dosing regimens from published literature did not reach ≥ 90% PTA.
- Mean levofloxacin clearance and half-life were 4.39±1.1 L/h and 16.74±6 h during SHIFT RRT. CRRT clearance and non-renal clearance were 2.91+0.9 L/h and 1.48+0.7 L/h, respectively.

Results (continued)

Table 2. PTA in 5000 Virtual Patients Receiving 10-Hour SHIFT Hemodialysis with Different Levofloxacin Regimens

Dosing	Early SHIFT RRT	Late SHIFT RRT
	PTA (Mean AUC24h/MIC > 50)	PTA (Mean AUC24h/MIC > 50)
500 mg Q 48 H	0.34	0.43
500 mg Q 24 H	0.70	0.78
750 mg LD, then 500 mg Q 48 H	0.56	0.65
750 mg LD, then 250 mg Q 48 H Post SHIFT	0.65	0.61
750 mg LD, then 500 mg Q 48 H Post SHIFT	0.91	0.78
750 mg LD, then 250 mg Q 24 H Post SHIFT	0.85	0.81
750 mg LD, then 500 mg Q 24 H Post SHIFT*	**0.98**	**0.92**
750 mg LD, then 750 mg Q 24 H Post SHIFT	0.99	0.94

*the lowest dosing regimen yielding ≥ 90% PTA

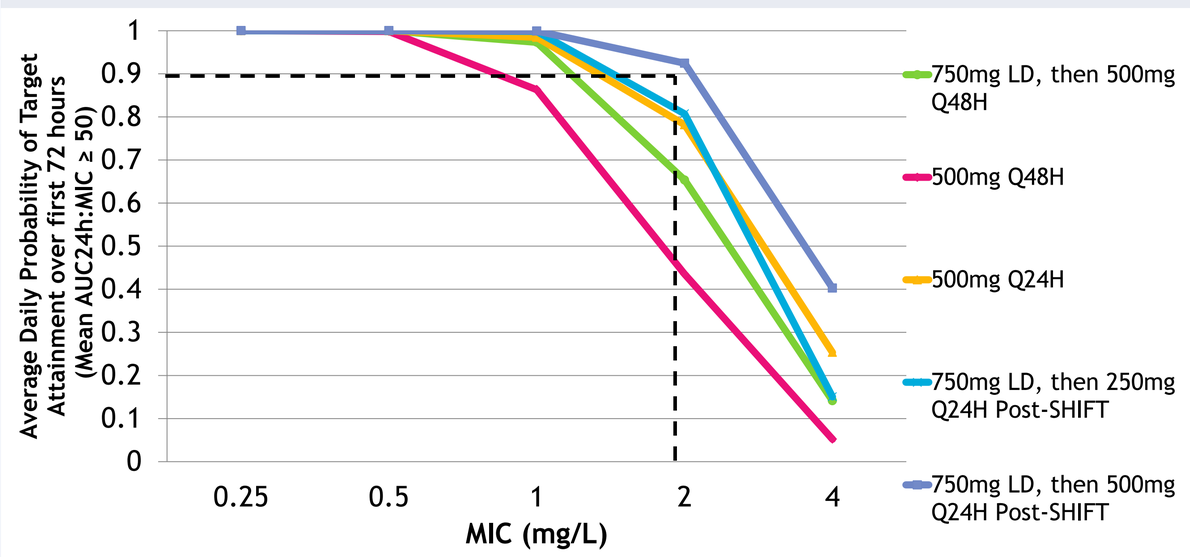


Figure 2. PTA of Selected Levofloxacin Regimens at Different MICs in Patients Receiving 10-Hour Late SHIFT Hemodialysis.

Discussion/Conclusion

- This is the first study using MCS to identify the optimal dose of levofloxacin for S. *pneumoniae* infections in critically ill patients receiving SHIFT RRT.
- A levofloxacin dose of 750 mg loading dose with 500 mg every 24 hours post-SHIFT is recommended in acute kidney injury patients receiving SHIFT RRT who have *Streptococcus pneumoniae* infections.
- A loading dose is required to reach the PTA in the first day of antibiotic therapy.
- Levofloxacin doses for Gram negative infections that have higher PD targets would require much higher doses to achieve ≥ 90% PTA.
- Application of our dosing recommendation should be limited to critically ill patients receiving SHIFT RRT with similar parameters as the virtual patients.
- Clinical validation of these finding from MCS is required to appropriately recommend antibiotic regimens in these patients.

References

1. Malone RS, et al. *Antimicrob Agents Chemother*. 2001; 45(10): 2949-54.
2. Aronoff GR, et al Drug Prescribing in Renal Failure : Dosing Guidelines for Adults. Philadelphia, Pa. :American College of Physicians, 2007. Print.
3. Seyler L, et al. *Crit Care*. 2011; 15(3):R137.
4. Goldstein S, et al. *Pediatr Nephrol. 2001; 16:* 1015-8.
5. Lannini PB. *Expert Opin Drug Safety*. 2002; 1(2): 121-8.
6. Lui HH. *Drug Saf*. 2010; 33(5): 353-69.
7. Hansen E, et al. *Intensive Care Med*. 2001; 27: 371-5.
8. Guenter SG, et al. *Pharmacotherapy*. 2002; 22(2): 175-83.
9. Clinical and Laboratory Standards Institute. Wayne, PA:*CLSI*;2014.
10. Forrest A, et al. *Antimicrob Agents Chemother*. 1993; 37(5): 1073-81.
11. Craig WA. *Clin Infect Dis*. 1998;26(1):1-10.

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