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# Model based optimization of Daptomycin dosing during high – intensity renal replacement therapy

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## ABSTRACT/REVISED

**Objectives:** Daily intermittent hemodialysis (IHD) is a renal replacement therapy (RRT) option that may be used to treat patients when the target dose of RRT cannot be provided with the conventional every other day schedule. The objective of this study was to establish the optimal dosing regimen of Daptomycin (DAP) for the treatment of serious gram positive infections during daily IHD.

**Methods:** Population pharmacokinetic (popPK) models of DAP in IHD patients and patients with bacteremia were used in this analysis. Daily doses of 3 and 4 mg/kg given 1 hour prior, 1 hour into, and 1 hour before the end of dialysis were evaluated with Monte Carlo Simulation (MCS, n=10000) to assess for the magnitude of drug exposure with daily 2, 3, 4, and 5 hours IHD sessions. To select the optimal regimen based on the duration of dialysis provided, the simulated mean $\pm$ SD trough levels at 72 hours and $AUC_{48h\text{-}72h}$ in dialysis were compared with the simulated mean $\pm$ SD trough levels at 72 hours and $AUC_{48h\text{-}72h}$ for the dose of 6 mg/kg every 24 hours using the popPK model developed in the bacteremia trial.

**Results:** Manufacturer recommended 6 mg/kg DAP regimens should result in mean $\pm$ SD trough levels and $AUC_{48h\text{-}72h}$ values of 9.5 + 8.1 µg/ml, and 441.1 $\pm$ 275 mg.h/L, respectively. Comparing these means with those expected to be achieved by the suggested daily dialysis regimens, percentage differences of 38% to 64%, and - 5% to 14% in magnitude were noted, for trough levels and $AUC_{48h\text{-}72h}$ values, respectively. Summary of optimized dosing recommendations are presented in Table 1.

| Timing of drug administration | Length of daily dialysis session (hours) | | | |
|---|---|---|---|---|
| | 2 | 3 | 4 | 5 |
| 1 h prior to dialysis | 3 mg/kg | 3 mg/kg | 4 mg/kg | 4 mg/kg |
| 1 h into dialysis | 3 mg/kg | 3 mg/kg | 4 mg/kg | 4 mg/kg |
| 1 h before the end of dialysis | 3 mg/kg | 3 mg/kg | 3 mg/kg | 3 mg/kg |

**Conclusion:** We conclude that the DAP dosing strategies presented here would provide adequate coverage from the efficacy standpoint in daily IHD, as compared to the exposure achieved by the patients of bacteremia trial. Our analysis also showed a definite increase in the magnitude of the expected trough levels using these methods of dosing DAP, which may lead to an increase in the probability of drug related adverse events. Clinicians should carefully weigh risks and benefits of all treatment related effects when managing their patients with the above suggested dosing regimens.

## INTRODUCTION

RRT has dramatically evolved during the past couple of decades and is often individualized to patient specific clinical status and tolerance. As the patient's condition changes, the strategy for RRT should be frequently altered to meet the current clinical needs and to maintain efficacy. Technical aspects of IHD, including the length of dialysis, may have significant effects on the extent by which a drug is removed during dialysis. Drugs that are known to be removed by IHD to a meaningful degree may result in fluctuating levels as a consequence of the changes in dialysis length or intensity, and provide inadequate systemic drug exposure.[1] DAP clearance during IHD using high – flux membranes has been shown to be similar, while during the off – dialysis period is reduced by about 75%, as compared to the clearance by the patients in the bacteremia and infective endocarditis trial.[2] It was suggested for clinicians to consider the dose of 9 mg/kg instead of 6 mg/kg when the interdialytic period is about 72 hours to ensure drug exposures comparable to the 48 hours interdialytic periods. Others investigated the relationship between daptomycin exposure and the probabilities of CPK elevations.[3] Based on their findings, $C_{min}$ at the breakpoint of 24.3 mg/L was most significantly associated with clinically important CPK elevations. The aim of our work was to use Monte Carlo simulation to evaluate the magnitude of daptomycin exposure and resulting trough levels when select doses are given 1 hour prior, 1 hour into, and 1 hour before the end of dialysis. Then, we compared the exposures and trough levels with that of the model from the bacteremia and endocarditis trial to select the dosing method that may be considered most appropriate for daily administration.

## METHODS

**Monte Carlo Simulation**

- Monte Carlo Simulation with Pmetrics (V.0.25), without covariance matrices and 2 compartment IV pharmacokinetic models characterized by:[4]

| Parameter | Mean (SD) value for model | |
|---|---|---|
| | IHD[5] | B-IE[2] |
| $V_C$ (L) | 5.52 (1.90) | 6.56 (3.10) |
| CL (L/h) | 0.24 (0.06) | 0.96 (0.47) |
| $K_{12}$ ($h^{-1}$) | 1.61 (1.91) | 1.67 (3.94) |
| $K_{21}$ ($h^{-1}$) | 1.17 (1.13) | 1.34 (3.40) |
| $CL_{HD}$ (L/h) | 1.30 (0.63) | NA |

$V_C$, volume of the central compartment; CL, nondialytic clearance of DAP from the central compartment; $K_{12}$, transfer rate constant from the central to the peripheral compartment; $K_{21}$, transfer rate constant from the peripheral to the central compartment; $CL_{HD}$, hemodialysis clearance of DAP from the central compartment

- Patient weights for simulation was obtained from anthropometric reference data for children and adults in the United States and was simulated with a discrete distribution.[6]
- Daily doses of 3 and 4 mg/kg given 1 hour prior, 1 hour into, and 1 hour before the end of dialysis were evaluated for exposure, then compared with the exposure likely to be achieved by patients with similar body weights using the population pharmacokinetic model developed in the bacteremia and infective endocarditis trial. The simulated mean $\pm$ SD trough levels and $AUC_{48h\text{-}72h}$ served as the bases of comparison for the two populations.

## RESULTS

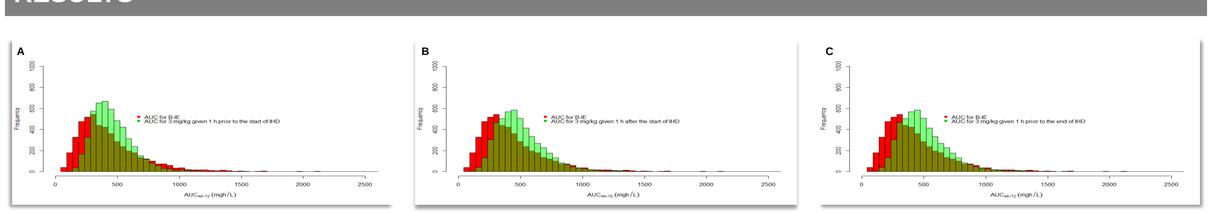



**Figure 1. A – C Histograms of simulated $AUC_{48h\text{-}72h}$ for B – IE model and 2 hours daily intermittent hemodialysis sessions**

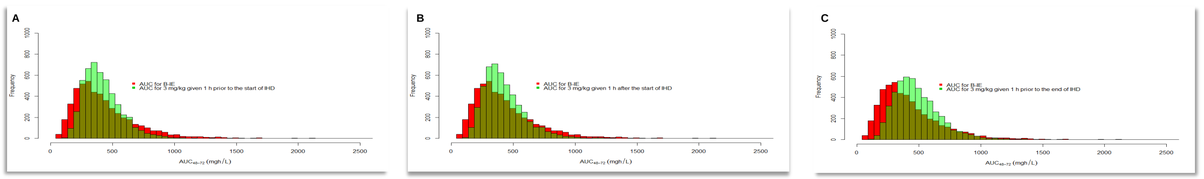



**Figure 2. A – C Histograms of simulated $AUC_{48h\text{-}72h}$ for B – IE model and 3 hours daily intermittent hemodialysis sessions**

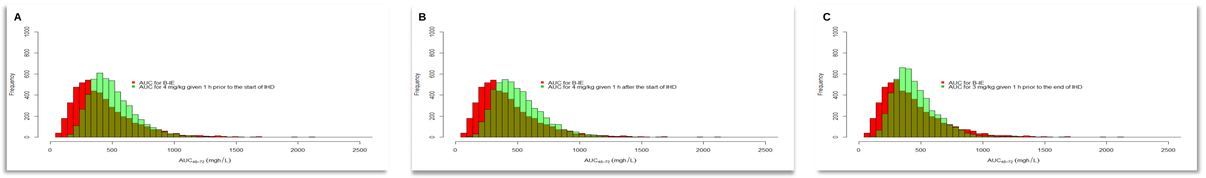



**Figure 3. A – C Histograms of simulated $AUC_{48h\text{-}72h}$ for B – IE model and 4 hours daily intermittent hemodialysis sessions**

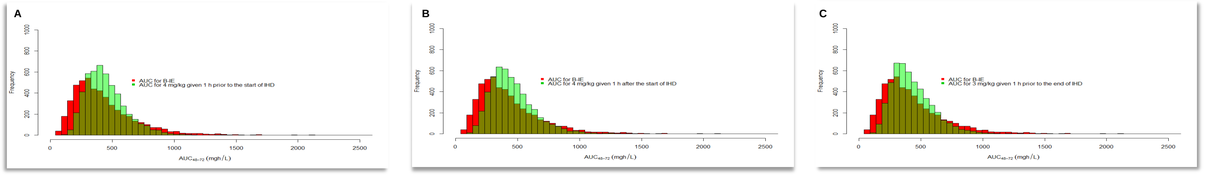
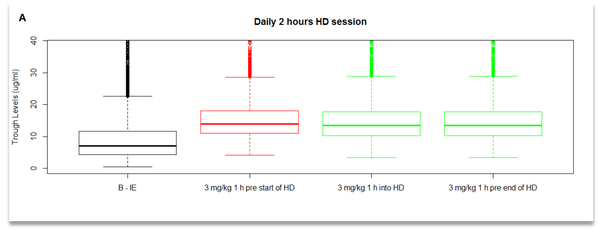
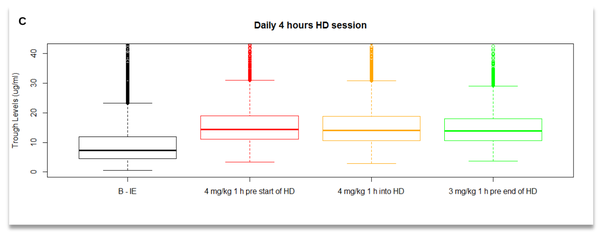



**Figure 4. A – C Histograms of simulated $AUC_{48h\text{-}72h}$ for B – IE model and 5 hours daily intermittent hemodialysis sessions**

## RESULTS







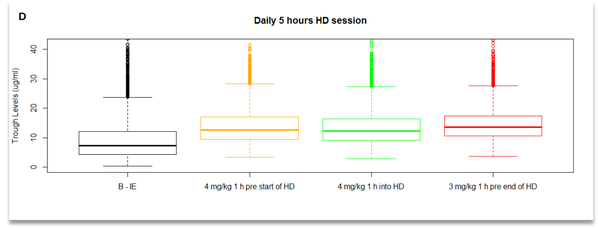




**Figure 5. A – D Box plots of simulated Trough levels at 72 hours**

## CONCLUSION

- Dosing of DAP for the treatment of serious infections in daily intermittent hemodialysis greatly depends on the length of dialysis treatment and the timing of drug administration. For dialysis sessions lasting from 2 to 5 hours daily, 3 and 4 mg/kg dosages would be sufficient to ensure likely adequate mean $\pm$ SD $AUC_{48h\text{-}72h}$ values. The perhaps best strategies for administration times are to give the dose 1 hour after the start of or 1 hour before the end of the dialysis session.
- As a result of decreased DAP clearance while off dialysis, practitioners should be aware of the increased chance for drug accumulation when DAP is given according to these dosing methods. After 72 hours of therapy, the mean value for trough concentrations may reach levels of up to 64% higher, as compared to patients with normal renal function.

## REFERENCES

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