# Novel Method to Maximize Levofloxacin Pharmacodynamics for the Treatment of Systemic Gram Negative Infections Based on the Population Distribution of Patient Demographics at a Community Hospital

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## ABSTRACT/INTRODUCTION

**Background:** Levofloxacin (LVX) is an antibiotic with limited susceptibility profile against gram negative organisms. The aim of our study was to develop institution specific LVX dosing guidelines based on the patient demographics and the Minimum Inhibitory Concentration (MIC) distribution of gram negative isolates known to cause systemic infections at a community hospital.

**Methods:** Previously published population pharmacokinetic model in patients with various degrees of renal function was used in this analysis. Probability of Target Attainment (PTA) was established with Monte Carlo Simulation (MCS) for MIC ranges of 0.125 to 1 ug/mL. Then, Cumulative Fraction of Response (CFR) was calculated targeting an Area Under the Curve ($AUC_T$)/MIC ratio of at least 125 for package insert (PI) recommendations. Additionally, alternative dosing intervals were evaluated to assess their population PTA. The degree of change in drug accumulation with the alternative dosing intervals was estimated to assess for it's magnitude by comparing the median, 5th and 95th percentiles of minimum plasma concentrations ($Cp_{min}$) for 750 mg LVX q24h at the CrCl of 51 ml/min with the $Cp_{min}$s for the alternative dosing regimens at the respective renal function categories.

**Results:** PI LVX dosing regimens are expected to achieve suboptimal CFR at all renal function categories. The MCS also showed that meaningful PTAs cannot be achieved by conventional dosing for MICs higher than 0.5 ug/ml. Estimated CFRs showed minimal improvement when LVX regimens with a PTA of 0.9 or more at an MIC of 0.25 ug/ml were compared with regimens reaching a PTA of 0.9 or more at an MIC of 0.5 ug/ml. Drug accumulation using alternative dosing intervals is expected to be similar or less in magnitude than the estimated $Cp_{min}$ median, 5th and 95th percentiles for the 750 mg LVX q24h at CrCl of 51 ml/min.

**Conclusion:** We conclude that for the treatment of systemic gram negative infections to achieve the optimal pharmacodynamic (PD) index of $AUC_T$/MIC of > 125 with LVX in our patient population, the PI approved dosing regimens provide insufficient coverage. Moreover, based on the PD profile of LVX, treatment of systemic gram negative infections would require the use of more frequent dosing intervals for isolates with an MIC of 0.5 ug/ml, while optimal treatment of an organism with a LVX MIC of more than 0.5 ug/ml would require the use of an alternative agent.

## MATERIALS AND METHODS

**Pharmacokinetic Parameter Estimates**

- Previously published pharmacokinetic (PK) model derived from patients with serious community acquired infections was extracted from the literature[1].
- Demographic data from patients previously admitted to Nyack Hospital was used in the analysis (**Figure 1.**)

**Microbiological Susceptibility Data**

- Obtained from Nyack Hospital's ongoing surveillance program (2010 – 2011)

**PK/PD Index**

- $AUC_T$/MIC of 125 or more seemed to best correlate with efficacy of fluoroquinolone[2,3], and was utilized as the goal of therapy

**Monte Carlo Simulation**

- A two compartment model with first order output was used to model time-concentration profiles
- Pharmacokinetic parameter estimates for each simulated patients were based on point estimates of individual CL, $Vd_1$, $Vd_2$, $K_{12}$, and $K_{21}$ using CrCl, age, race, body weight, and site of infection as the explanatory variables in a previously published population model[1] and their respective CV as the measure of dispersion.
- Demographic variables were assumed to follow uniform, discrete or Weibull, while all PK parameters were assumed to follow lognormal distribution
- Monte Carlo Simulation was performed at 5000 replicates using the Crystal Ball program

## RESULTS

### Figure 1: Population Distribution of Age and Race

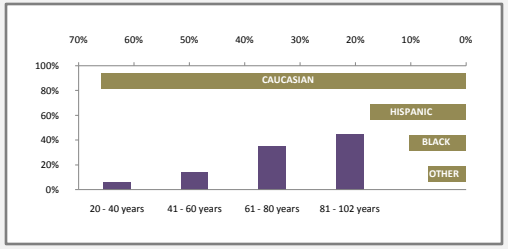


**Figure 1.** shows the demographics of the 64 patients used in the analysis. The majority of the patients in the group were Caucasian, followed by Hispanic and Black. The group Other consisted mostly of patients with Asian descent. Most of the patients age was between 61 and 102 years, with a population mean ± SD of 74.6 ± 17.9 years.

## RESULTS

### Figure 2: MIC Distribution and Microbiology of Systemic G - Bacteria

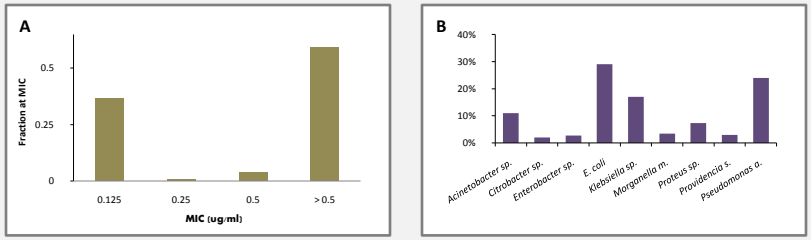


**Figure 2. A** shows the MIC distribution of 259 gram negative bacteria known to cause systemic infections at Nyack Hospital. Most common diagnosis encountered during the treatment of these organisms were Pneumonia (39%), Blood Stream Infections (17%), Skin and Skin Structure Infections (15%), Pyelonephritis (9%), Intra Abdominal Infections (8%) and Other Systemic Gram Negative Infections (12%). **Figure 2. B** shows the break down of bacterial geneuses and species of the 259 clinical isolates. *Acinetobacter sp., E. coli, Klebsiella sp.,* and *Pseudomonas aeruginosa* were isolated most often during this observation period.

### Figure 3: Probability of Target Attainment at Different Levels of Renal Function

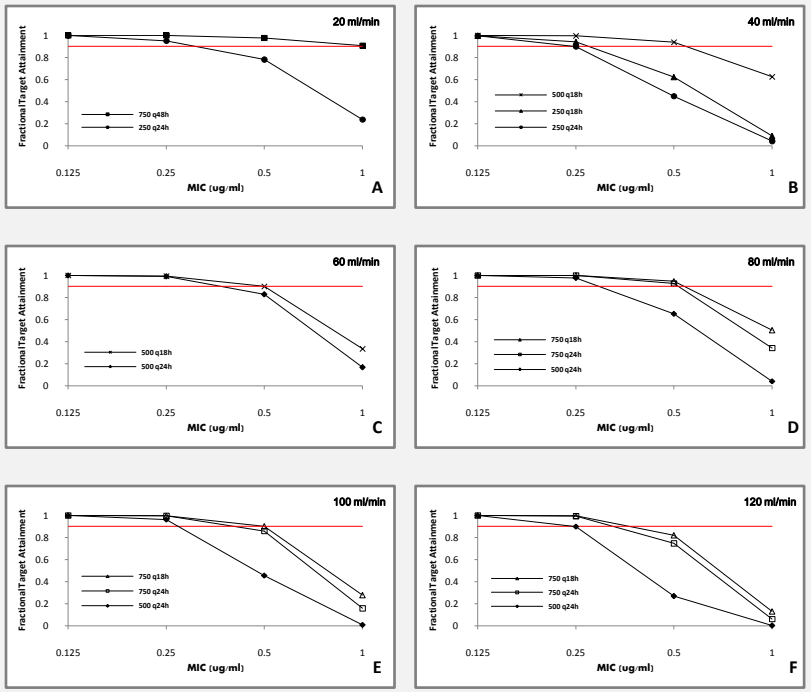


**Figure 3. A trough F** shows the Probability of Target Attainment of LVX PI approved dosing regimens and PI doses at alternative dosing intervals. The red line in the figures represents the PTA of 0.9 at the respective MIC needed to achieve optimal therapy. The PTA of all doses and respective dosing intervals below that line in considered suboptimal. The point of interest in these figures is that no PI approved regimen achieves meaningful PTA at the MIC of 1 or more. At present time, the CLSI approved break point for LVX for gram negative organisms is 2 ug/ml, while the pharmacodynamic profile of LVX allows for acceptable PTA only up to an MIC of 0.5 ug/ml. Therefore, for MICs > 0.5, the use of an alternative agent will be considered.

## RESULTS

### Figure 4: Summary statistics of simulated $Cp_{min}$ values

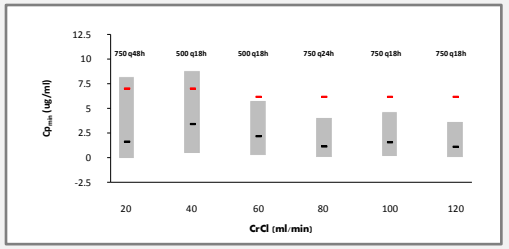


**Figure 4.** shows the median (▬), 5th through 95th percentiles (grey boxes) of simulated $Cp_{min}$ statistics for PI doses and recommended alternative dosing intervals to achieve a PTA of 0.9 or more at the MIC of 0.5 ug/ml at various levels of renal function compare to the 95th percentiles of $Cp_{min}$ (▬) achieved by the PI approved 750mg q24h at the CRCl of 51 ml/min. LVX trough levels with alternative dosing strategies are expected to achieve similar magnitude compared to the PI recommended maximum dose and respective dosing interval at the CrCl of 51 ml/min.

### Table 1: Population Probability of Target Attainment

| CrCl (ml/min) | CFR (%) for Regimen Evaluated | | | |
|---|---|---|---|---|
| | MIC ≤ 0.25 ug/ml | | MIC ≤ 0.5 ug/ml | |
| 20 | 250 mg q24h | 36.8 | 750 mg q48h | 39.8 |
| 40 | 250 mg q18h | 36.7 | 500 mg q18h | 40.4 |
| 60 | 500 mg q24h | 36.9 | 500 mg q18h | 40.3 |
| 80 | 500 mg q24h | 36.9 | 750 mg q24h | 40.5 |
| 100 | 500 mg q24h | 36.8 | 750 mg q18h | 40.3 |
| 120 | 750 mg q24h | 36.9 | 750 mg q18h | 40 |

### Table 2: Revised Dose Adjustment Guidelines

| CrCl (ml/min) | MIC (ug/ml) | | | |
|---|---|---|---|---|
| | ≤ 0.125 | ≤ 0.25 | ≤ 0.5 | > 0.5 |
| | Optimal LVX Dose and Dosing Interval | | | |
| 20 | 250 mg q24h | 250 mg q24h | 750 mg q48h | Use of an alternative agent is strongly recommended |
| 40 | 250 mg q24h | 250 mg q18h | 500 mg q18h | |
| 60 | 500 mg q24h | 500 mg q24h | 500 mg q18h | |
| 80 | 500 mg q24h | 500 mg q24h | 750 mg q24h | |
| 100 | 500 mg q24h | 500 mg q24h | 750 mg q18h | |
| 120 | 500 mg q24h | 750 mg q24h | 750 mg q18h | |

## CONCLUSION

- Simulation results suggest that the PI approved dosing regimens provide suboptimal population PTA at all levels of renal function considering LVX activity against the pathogens evaluated.
- The chance of achieving meaningful PTA at the MIC of 1 or more with PI approved doses and dosing intervals is very unlikely, therefore empiric dosing adjustments should focus on MICs of < 1 ug/ml.
- Due to the lack of significant benefit observed with the alternative dosing intervals, targeting the MIC of 0.5 ug/ml for empirically is not justified based on the MIC distribution encountered in this analysis. Consequently, empiric dosing will be based on targeting the MIC of 0.25 ug/ml, while dose adjustments will be recommended upwards for MICs of 0.5 ug/ml based on susceptibility reports.
- For MICs of more than 0.5 ug/ml, the use of an alternative agent is strongly recommended .

## REFERENCES

1. Preston S, Drusano G, Berman A, et al. Levofloxacin population pharmacokinetics and creation of a demographic model for prediction of individual drug clearance in patients with serious community-acquired infections. Antimicrobial Agents Chemother 1998, 42 (5): 1098 - 1104
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