EP001

# Population Probability of Target Attainment of Colistin at Different Levels of Renal Function Against *Pseudomonas aeruginosa* and *Acinetobacter baumanii* in Europe

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## ABSTRACT

**Objectives:** Pharmacodynamic evaluation of anti-infective agents via Monte Carlo simulation (MCS) and organism specific MIC distribution is a useful approach to characterize the target attainment of empiric dosing regimens. The aim of this study was to establish the population probability of target attainment (PTA) of starter Colistin (CST) dosing regimens derived using the Garonzik et al. clinical equations for the treatment of critically ill patients with pulmonary infections in Europe.

**Methods:** Pharmacokinetic model of CST established in critically ill patients and EUCAST MIC distributions of *Pseudomonas aeruginosa* and *Acinetobacter baumanii* isolates in Europe were used in this analysis. Free concentrations of CST were calculated using a non-linear protein binding model. Doses up to 300 mg CST base activity per day were evaluated for population PTA with MCS (n=5000) at different levels of renal function for the MIC ranges of 0.0625 to 8 mg/L. Cumulative Fraction of Response (CFR) was calculated for each regimen targeting the *ƒ*AUC/MIC ratios necessary to achieve a killing of 1 and 2 log10 CFU derived from neutropenic mouse lung infection models.

**Results:** Empiric dosing regimens suggested by the Garonzik equations are expected to achieve the CFR < 85% for the killing of 1 and the CFR < 60% for the killing of 2 log10 CFU against both organisms at all levels of kidney function from 20 to 120 ml/min. When the CFRs were compared for the two organisms at 20 ml/min renal function intervals, an average of 7.7% and a 23.9% higher success rate was observed against *Acinetobacter baumanii* at the kill targets evaluated. The MCS also showed that these clinical equations based dosing recommendations with the suggested maximum daily dose of 300 mg CST base activity result in a sharp fall of the population PTAs empirically for patients in the normal renal function category. The magnitude of this decline was realized by a difference of up to -32% in CFRs at normal renal function as compared to mild renal impairment.

**Conclusion:** We conclude that for the treatment of serious *Pseudomonas aeruginosa* and *Acinetobacter baumanii* lung infections to achieve the killing of 1 and 2 log10 CFU, the dosing approaches based on the Garonzik equations provide suboptimal population PTAs, especially in patients with normal renal function. To improve target attainment of CST for the treatment of critically ill patients, the use of alternative dosing approaches allowing for higher daily doses, or applying combination therapy should be considered. A careful evaluation of the balance between the risk of toxicity and expected clinical benefit must be considered before implementation of such alternative dosing strategies.

## INTRODUCTION

CST is a polypeptide antibiotic comprised mainly of CST A and CST B, that was first introduced in the 1950s, and later replaced by other antibiotics that were less toxic. In the past decade there has been an increasing emergence of multidrug resistant gram negative pathogens, especially worrisome in the management of critically ill patients. In the current era, which is lacking significant advances in new antimicrobial development, CST has resurfaced as a treatment option and often is the only active agents against this group of highly resistant organisms[1]. In vivo lung experiments have shown that the $\int AUC_{24h}$/MIC was most closely related to the antimicrobial effect of CST with a 2 log kill target values of 36.9 to 45.9 and 22.5 to 95 for *Pseudomonas aeruginosa* and *Acinetobacter baumanii*, respectively[2,3]. Recent advancement in assay development of CST and the prodrug CST methanesulfonate now allows researchers to better characterize the disposition of these chemical entities in the bodily fluids of critically ill patients. Ganronzik et al. studied the pharmacokinetics of CST in critically ill patients at different levels of renal impairment[4]. Population pharmacokinetic parameters were established for CST and CST methanesulfonate. Then, these parameters were used to derive a set of equations designed to provide dosing recommendations for CST at the bedside. The aim of our work was to use MCS to integrate PK derived using the Garonzik et al. equations and PD with microbiology data to yield population PTA of CST at different levels of renal function against the MIC distribution of recently reported *Pseudomonas aeruginosa* and *Acinetobacter baumanii* isolates for the treatment of critically ill patients with pulmonary infections in Europe[5].

## METHODS

**Monte Carlo Simulation**

- 5000 trial MCS was completed using ID – ODS™, an application for pharmacodynamic analysis of drugs coded in the R® software environment for statistical computing and graphics[6,7]
  - CST loading and maintenance dosing regimens were established using the bedside equations by Garonzik et al. with a maximum of 300 mg/24h administered at 12 hour intervals with a target CST concentration of 2.5 µg/ml
  - Total body $CL_{CST}$ estimates for each simulated patients were based on using the explanatory variable of creatinine clearance (CrCl)
  - Volume of the central compartment was estimated as a function of the body weight
  - CrCl was fixed at 20 ml/min intervals between the ranges of 20 to 120 ml/min during simulations
  - All pharmacokinetic parameter estimates were assumed to follow lognormal distribution
  - Protein binding was calculated with a non-linear protein binding model[8]
  - The mixed model of one and two compartments by Garonzik et al. characterizing the disposition of CMS and CMS methasulfonate in the body of critically ill patients was used to estimate concentration – time profiles for each simulated patient at 6 minutes increments until steady state was reached
  - The trapezoidal rule was used to calculate AUC, then the AUC was divided by the MIC to obtain the value for the desired PK/PD Index of the selected time interval
- Pharmacodynamic Target
  - PK/PD Index of the free drug AUC/MIC ratio necessary to achieve 1 $\log_{10}$ kill and 2 $\log_{10}$ kill in the lung was utilized as the goal of evaluation
- Population Probability of Target Attainment
  - Cumulative Fraction of Response was calculated for select regimen evaluated by multiplying the Probability of Target Attainment at the given MIC with the percentage of isolates found at that MIC, then the sum of this data yielded the CFR for the simulated regimen

| Organism | Percent Occurrence at CST MIC (µg/ml) of: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ≤ 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 |
| P. aeruginosa | < 0.1 | <0.1 | 2.3 | 21.7 | 42.4 | 27.7 | 3.3 | 2.5 |
| A. baumanii | 0 | <0.1 | 36.1 | 22.0 | 29.6 | 6.5 | 0.6 | 5.2 |

Table 1. CST MIC Distribution of *P. aeruginosa* and *A. baumanii* Isolates

## RESULTS

| | Renal Function Category Based on CrCl (ml/min) | | | | | |
|---|---|---|---|---|---|---|
| | 20 | 40 | 60 | 80 | 100 | 120 |
| $\int AUC_{0-24}$ (mg/l*hr) | 32.85 (26.43, 38.24) | 31.24 (23.45, 39.16) | 29.8 (21.43, 39.18) | 22.88 (15.84, 31.00) | 18.06 (12.21, 25.08) | 14.62 (9.70, 20.69) |

Table 2. Summary statistics of simulated CST $\int AUC_{0-24}$ at steady state [data presented as median (25th percentile, 75th percentile)]

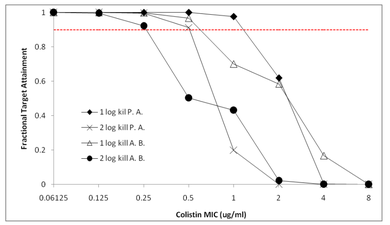


Figure 1 A. CST PTA at CrCl of 20 ml/min

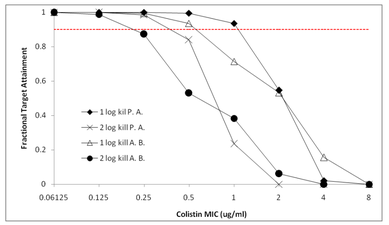


Figure 1 B. CST PTA at CrCl of 40 ml/min

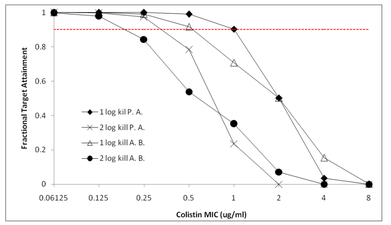


Figure 1 C. CST PTA at CrCl of 60 ml/min

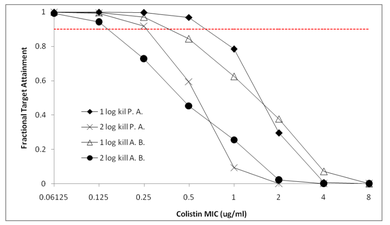


Figure 1 D. CST PTA at CrCl of 80 ml/min

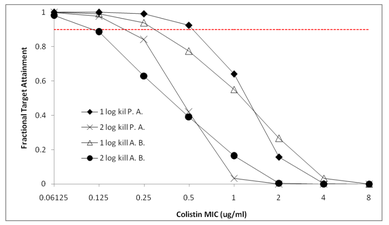


Figure 1 E. CST PTA at CrCl of 100 ml/min

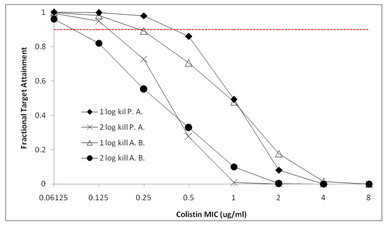


Figure 1 F. CST PTA at CrCl of 120 ml/min

## RESULTS

| CrCl (ml/min) | Killing | Dosing Interval | CFR (%) |
|---|---|---|---|
| 20 | 1 log kill | every 12 hours | 83.0 |
| | 2 log kill | | 31.1 |
| 40 | 1 log kill | every 12 hours | 79.3 |
| | 2 log kill | | 31.0 |
| 60 | 1 log kill | every 12 hours | 76.6 |
| | 2 log kill | | 29.8 |
| 80 | 1 log kill | every 12 hours | 65.3 |
| | 2 log kill | | 19.6 |
| 100 | 1 log kill | every 12 hours | 54.3 |
| | 2 log kill | | 13.0 |
| 120 | 1 log kill | every 12 hours | 44.6 |
| | 2 log kill | | 8.6 |

Table 4. CFR for CST regimens to achieve respective target killing for *Pseudomonas aeruginosa*

| CrCl (ml/min) | Killing | Dosing Interval | CFR (%) |
|---|---|---|---|
| 20 | 1 log kill | every 12 hours | 81.8 |
| | 2 log kill | | 57.4 |
| 40 | 1 log kill | every 12 hours | 81.1 |
| | 2 log kill | | 55.1 |
| 60 | 1 log kill | every 12 hours | 80.1 |
| | 2 log kill | | 53.4 |
| 80 | 1 log kill | every 12 hours | 74.5 |
| | 2 log kill | | 44.2 |
| 100 | 1 log kill | every 12 hours | 68.9 |
| | 2 log kill | | 36.4 |
| 120 | 1 log kill | every 12 hours | 63.0 |
| | 2 log kill | | 30.4 |

Table 5. CFR for CST regimens to achieve respective target killing for *Acintobacter baumanii*

## CONCLUSION

- For critically ill patients treated with CST to achieve the target 1 and 2 log kill free drug $AUC_{24h}$/MIC ratio derived from the neutropenic mouse lung models, the recommended doses and dosing intervals by the Garonzik et al. clinical equations provides suboptimal population probability of target attainment empirically against recently documented *Pseudomonas aeruginosa* and *Acinetobacter baumanii* isolates in Europe. The low CFRs calculated are especially pronounced at the normal renal function category, likely as a result of the maximum daily dose of 300 mg.
- To improve target attainment of CST for the treatment of critically ill patients, the use of alternative dosing approaches allowing for higher daily doses, or applying combination therapy should be considered. A careful evaluation of the balance between the risk of toxicity and expected clinical benefit must be considered before implementation of such alternative dosing strategies. The safety and efficacy of such regimens for the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumanii* lung infections must be validated by well controlled clinical trials.

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