Turn-over model characterizing effect of colistin on serum-creatinine in critically ill patients

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BACKGROUND

- Colistin is an old antibiotic used to treat multi-drug resistant infections. Colistin causes kidney toxicity [1], but no quantitative model has been developed to describe the PKPD-relationship.
- A tendency of protective effects of meropenem against colistin-associated kidney toxicity has been observed [2]
- A previous analysis [3] indicated a correlation between higher colistin exposure and a higher hazard of death. However, since colistin is nephrotoxic and its prodrug (CMS) is renally cleared, the analysis might be confounded by kidney function.
- We aimed to model the colistin-creatinine interplay

DATA FOR THIS ANALYSIS

① 356 patients (17–95 years) from the AIDA study [2]

② Gram-negative bacterial infections in all patients
- Carbapenem resistant (MIC ≥ 2mg/L)
- Colistin susceptible (MIC ≤ 2mg/L)

③ Patients in this analysis were not on dialysis

④ Intention-to-treat with CMS (colistin prodrug) in all patients
- 9 MU load, 4.5 MU (adjusted for kidney function) q12h
  30 min infusion, for 10 days

⑤ Intention-to-treat with meropenem in 49% (177/356) of patients
- 2 g (adjusted for kidney function) q8h
  3 h infusion

⑥ Serum creatinine was sampled before and at randomization, as well as 7, 14, and 28 days after randomization.

⑦ Daily colistin average concentrations ($C_{avg,\,daily}$) were predicted from a previously published PK model [3]

MODEL SIMULATIONS AND PREDICTIONS

- The model captures the change in serum creatinine over time (Figure 1). At the end of trial (day 28), the data is less variable than the model predicts.

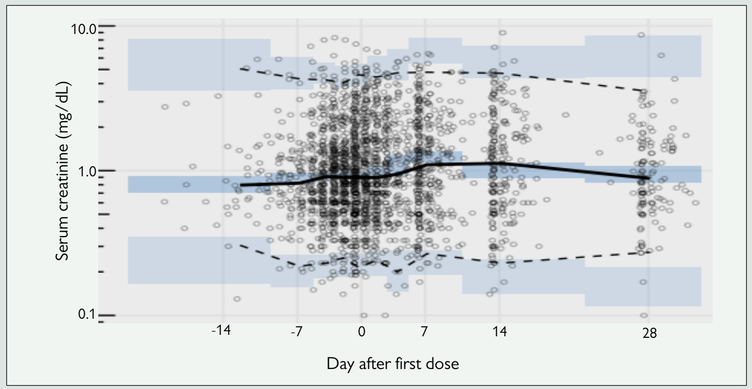

Fig 1. Visual predictive check (VPC) for model simulations (shaded areas) against clinical data (black circles). Black lines represent descriptive statistics of the data (solid = median, dashed = 95% CI). The width of the shaded areas represent 95% CI of simulations.

- Black lines (Figure 2) represent predictions from as-treated data of those patients still remaining in the study
- Colored lines (Figure 2) represent predictions from constant $C_{avg,\,daily}$

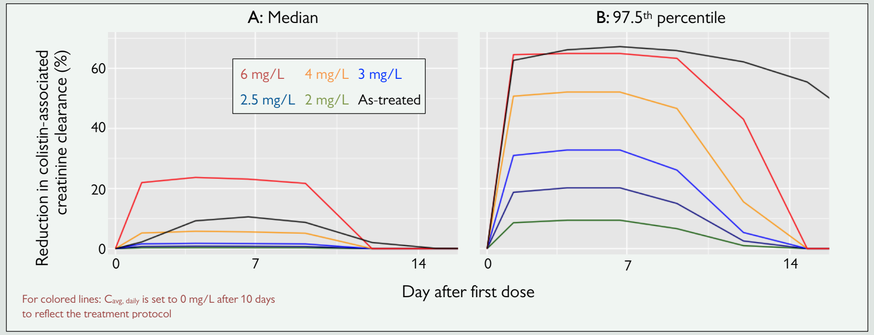

Fig 2. **A:** At 3 mg/L, median reduction in colistin-associated creatinine clearance (CLCR) is below 5%.
B: Increasing $C_{avg,\,daily}$ from 2 to 2.5 mg/L results in almost twice as high reduction in the 97.5th percentile of CLCR.

MODEL DESCRIPTION

- Time-varying serum creatinine (SCr) was described using a turn-over model
  - Baseline SCr was estimated using the first measurement (not used as an observation), while imposing the same random effect as on RUV
  - Cockcroft-Gault was used to estimate baseline CrCL from baseline SCr
- Impact of $C_{avg,\,daily}$ on creatinine clearance was described with a direct effect E_{max}-model: $I = \frac{C_{avg,\,daily}^{\gamma} \times I_{max}}{C_{avg,\,daily}^{\gamma} + I_{50}^{\gamma}}$, where I stands for *inhibition* of CLCR
- Disease progression of CLCR with time was described with a monotonically increasing/decreasing exponential function, towards an asymptotic plateau value describing a *change from CLCR baseline* ($\Delta_{CLCR_{baseline},\,\infty}$):

$$\Delta_{CLCR_{baseline}}(t) = \Delta_{CLCR_{baseline},\infty} \times (1 - e^{-\frac{\ln 2}{t_{½}} \times t})$$

MODEL PARAMETERS

	Typical value (RSE)	№	Inter-individual standard deviation (RSE)
$\Delta_{CLCR_{baseline},\,\infty}$: Disease progression asymptote	0.75 (10%)	1	1.01 (16%)
		correlation(1,2)	0.56 (20%)
$t_{½}$: Disease progression half-life (days)	19.78 (31%)	2	0.78 (16%)
		correlation(2,3)	-0.27 (30%)
I_{50}: Half I_{max} at this $C_{avg,\,daily}$ (mg/L)	6.82 (5%)	3	0.49 (9%)
I_{max}: Maximum inhibition on creatinine clearance	0.68 (4%)	4	-
γ: Sigmoidicity parameter	4.31 (9%)	5	-
Additive residual error (log-scale)	0.19 (3%)	6	0.34 (9%)

CONCLUSION

- Colistin-associated kidney toxicity might be sensitive to increases in already low (~2.5 mg/L) $C_{avg,\,daily}$
- A suggested upper limit of ~2.5 mg/L for $C_{avg,\,daily}$ would limit the reduction in CRLC to <20% in 97.5% of patients
- Meropenem did not significantly impact I_{50} or $\Delta_{CLCR_{baseline},\,\infty}$ ($p > 0.001$)

[1] Forrest et al. Antimicrob Agents Chemother. 2017; 61(11) [2] Paul et al. Lancet Infect Dis. 2018; 18(4):391–400 [3] Kristoffersson et al. Clin Microbiol Infec. 2020; 26(12):1644–1650