Background and Objective

In recent years, colistin has gained popularity as a last resort antibiotic in the battle against resistant bacteria. *Pseudomonas aeruginosa* is well known to develop resistance against multiple antibiotics and thus, there is a need to ensure proper dosing of colistin either as monotherapy or in combination with other antibiotics. As colistin is administered as CMS, a prodrug, there is a delay before efficient concentrations are obtained and a loading dose may be warranted.

The aim of this study was to develop a pharmacokinetic-pharmacodynamic (PKPD) model that describes the time course of the bactericidal activity of colistin against wild-type and resistant *P. aeruginosa* in vitro, and to investigate the bacterial kill after different dosing schedules based on PK in patients and the developed model.

Methodology

Time-kill curve experiments:
- In vitro time-kill curve experiments were conducted for 24 hours on two strains of *Pseudomonas aeruginosa*, wild-type (ATCC 27853), MIC of 1 mg/L, and a clinically isolated resistant-type (PL0603761) with MIC of 1.5 mg/L.
- Colistin exposure was at different initial concentrations ranging between 0.25-16 times the MIC. Actual colistin concentrations were measured at 0, 8 and 24 hours by LCMS-MS (1).
- Bacterial counts were monitored with frequent sampling and conducted in two to three replicates.

Data Analysis & Model Building:
- All log-transformed data were fitted simultaneously using NONMEM7 with LAPLACIAN and M3 method for handling data below level of detection.
- The semi-mechanistic model includes:
  - compartments for drug-susceptible, growing bacteria (S) and for susceptible, resting bacteria (R) with a breakpoint for turning on the rate of transfer of bacteria (kpe) between the two compartments (2,3),
  - different models for the apparent emergence of resistance were tested; a binding function that inhibits the power effect of colistin (3), a compensatory mutation function (4) or an estimated pre-existing fraction of resistant bacteria in the inoculum (5).
- Assumption of no variability between experiments but with quantified residual error accounting for replicates (L2) data item.

Predictions of dosing schedules:
Bacterial counts were predicted for a typical individual by allowing the concentrations predicted by a previously developed PK model for the prodrug, colistin methanesulfonate (CMS) and colistin (6) to drive the bacteria kill. Concentration-dependent protein binding was also accounted for based on an equation derived from an equilibrium dialysis study.

Results

Colistin binding:
- The measured colistin concentrations were 4.4–78% lower than the intended concentrations and there was a progressive reduction of the concentration with time due to unspccific binding of colistin to material and possible degradation during the experiments.

Fig. 1: PKPD model for colistin with developing resistance. The two CMS compartments (in grey box) were only utilised during predictions.

Model building: The developed model (Fig. 2) could describe the data for both strains of *P. aeruginosa*. The application of actual colistin concentrations and the rate of loss in the modeling was important in the characterization of the resistance-effect relationship.
- The emergence from non-resistance (NRe) to resistance (Re) in the experiments was best described by a binding function (4). The drug effect was best described by a power function; for wild-type: 6.2 X Conc^2.6 and for the resistant strain: 1.0 X Conc^2.2. The growth rate, k_grow, was 31% lower in the resistant strain.
- The rate of resistance development, k_r, was a linear function dependent on concentration with an assumption of no resistance reversibility for both strains.

Conclusions

The PKPD model for colistin described bacterial kill for both wild-type and resistant isolates.
- The model will be valuable in further exploration of potential dosing regimens for example longer infusion period or a higher maintenance dose (e.g. 4.5MU every 12 hours).
- For the resistant bacteria, clinical exposure would not be sufficient and a combination with other antibiotics is indicated.

References