**P0724**

**Paper Poster Session IV**

**Update on colistin & polymyxin B**

## Pharmacokinetic-pharmacodynamic modelling characterization of the initial bactericidal effect of colistin against *Pseudomonas aeruginosa* in a murine lung infection model

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**Objective.** Front loading dose strategy may be of value for the treatment of multidrug resistant (MDR) infections (1). Yet the lack of precise ways to assess the initial antimicrobial effect precludes rational dosing optimization. *In vitro* pharmacodynamics (PD) data may be mixed with *in vivo* pharmacokinetic (PK) data (2) but this approach needs to be validated, which constitutes the objective of this study.

**Methods.** *In vitro* kill curves experiments were conducted with *Pseudomonas aeruginosa* exposed to static concentrations of colistin ranging from 0.25 to 8 mg/L, and analyzed with various PD models (3). Mice were infected intrapulmonary with the same strain of *Pseudomonas aeruginosa* and treated with 10, 20 or 30 mg/kg of colistin administered subcutaneously. Mice were sacrificed at various time points (from 0 to 30h) in order to follow colistin pharmacokinetics (PK) and bacteria counts in lung with time. *In vivo* PK and *in vitro* PD models were merged to predict bacteria counts in mice and compare these values with those determined experimentally in mice.

**Results.** The selected *in-vitro* PD model was composed of two subpopulations with different susceptibility that developed adaptive resistance over time. The antimicrobial effect predicted by combining *in vitro* PD with *in vivo* PK was by many folds overestimated compared with the observed effect. Moreover the PD model selected *in vitro* led to identifiability problems and could not apply *in vivo*.

**Conclusion.** Combining *in vivo* PK with *in vitro* PD to predict the initial bactericidal effect of colistin against *Pseudomonas aeruginosa* in a murine lung infection model leads to a major over-estimation of the effect.

### References

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3. Jacobs M et al. Distinguishing antimicrobial models with different resistance mechanisms via Monte Carlo simulations and population pharmacodynamic modeling. Antimicrobial Agents and Chemotherapy, submitted. 2014.