# Translational PKPD modelling of ceftazidime/avibactam for treatment of carbapenemase-producing *Klebsiella pneumoniae* in the persistently neutropenic rabbit pneumonia model

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## Introduction

- **Translation of antimicrobial efficacy from preclinical to clinical** settings is complex and challenging for drug development (1).
- **24h murine infection models** are traditionally used to define pharmacokinetic-pharmacodynamic (PKPD) targets for antibiotics.
- A recent **14-day persistently neutropenic rabbit pneumonia model** has shown promise to better replicate clinical pneumonia and characterize disease progression (2).

## Aim

- **Translate the PK and PD of ceftazidime/avibactam** (CAZ/AVI) for the treatment of *Klebsiella pneumoniae* carbapenemase isolates, from *in vitro* time-kill curves to the persistently neutropenic rabbit pneumonia model using **PKPD modelling**.

## Methods

1. **CAZ/AVI plasma PK model** based on PK data from Petraitiene *et al.* (2).
   **CAZ/AVI single or multiple doses q8h** (60/15, 90/22.5 and 120/30 mg/kg as iv infusion) in healthy New Zealand White rabbits.
2. **CAZ/AVI PD effect model** adapted from *in vitro* model from Kristoffersson *et al.* (3).
3. **Prediction of lung bacterial burden (CFU/g)** based on **PK** and **PD models.**
   - Persistently **neutropenic rabbit pneumonia model**
   - Infection with KPC *K. pneumoniae* isolates (MIC= 1-2 mg/L).
   - Growth control & CAZ/AVI treatment group (120/30 mg/kg) for 7 or 14 days.
   - CAZ and AVI free fractions in plasma = 85% and 92%, respectively (4).
   - Drug effects driven by **free lung concentrations**, penetration ratio in lung = 24% and 22% of total CAZ & AVI plasma concentrations, respectively (5).
4. **Model predictions vs lung CFU at 7 and 14 days** observed by Petraitiene *et al.* (2). PD parameters were adapted to improve the translation of CAZ/AVI effect in rabbit.

## Results

### CAZ/AVI plasma PK model

- **Two compartment PK models** adequately described CAZ and AVI plasma PK profiles in healthy rabbits. Model included interindividual variability in clearance and peripheral volume for CAZ, and in central and peripheral volumes for AVI (Figure 2).

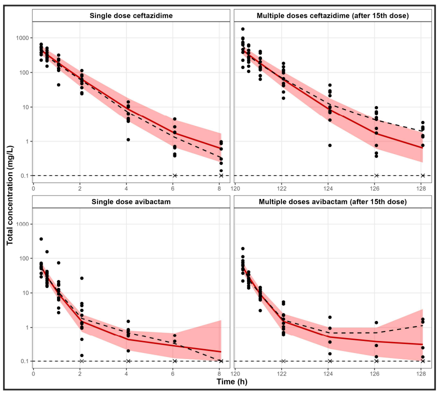


**Figure 2.** Prediction-corrected VPC of concentrations over time stratified by compound and administration.
Dots: observed concentrations, cross: concentrations below limit of quantification (0.1 mg/L), black dashed line: median percentile of observations, red line: median percentile of simulations, red area: 95% confidence interval around the median

- CAZ and AVI were rapidly eliminated with **terminal half-lives of 0.62 h and 0.29 h**, respectively.
- PKPD targets achieved by a CAZ/AVI dosing regimen of 120/30 mg/kg q6h
  - **fCAZ T>MIC$_{2mg/L}$** = 77% (plasma), 63% (lung)
  - **fAVI T>CT$_{1mg/L}$** = 34% (plasma), 17% (lung)

### Lung CFU prediction in infected rabbit

- Without any adaptation of the parameters, lung CFU at 7 and 14 days in the growth control and in the CAZ/AVI treated groups were poorly predicted by the *in vitro* PD model.
- PD parameters related to **bacterial growth** and **bacterial density** were adapted based on *in vivo* observations to improve the translation (Table 1).
- Re-estimation of bacterial growth ($K_{growth}$) and drug efficacy ($SLOPE_{CAZ}$ and $SLOPE_{AVI}$) improved *in vivo* predictions at 7 and 14 days.
- ***In vivo* $k_{growth}$, CAZ and AVI effects were reduced by 67%, 81% and 87% respectively compared to *in vitro*.**

**Table 1.** *In vitro* PD parameters and estimated parameters for *in vivo* translation

| PD parameter | *In vitro* model | *In vivo* translation |
|---|---|---|
| **BMAX** (system carrying capacity) | 9.8 $log_{10}$ CFU/mL | 3.2 log10 CFU/g* |
| **$k_{growth}$**(bacterial growth rate) | 1.4 $h^{-1}$ | 0.59 $h^{-1}$ |
| **$BN_{50}$** (bacterial density at 50% of $k_{BLasemax}$)[1] | 4.5 $log_{10}$ CFU/mL | 1.5 $log_{10}$ CFU/g* |
| **$BNI_{50}$** (bacterial density at 50% of $Slope_{AVI\_1}$)[2] | 6.9 $log_{10}$ CFU/mL | 2.3 $log_{10}$ CFU/g* |
| **$SLOPE_{CAZ}$** (CAZ effect) | 0.024 $h^{-1}$ | 0.0045 $h^{-1}$ |
| **$SLOPE_{AVI}$** (AVI effect) | 0.94 L/mg·h | 0.12 L/mg·h |

* Fixed parameter; [1] Model describing CAZ degradation by beta-lactamase; [2] Model describing AVI killing effect

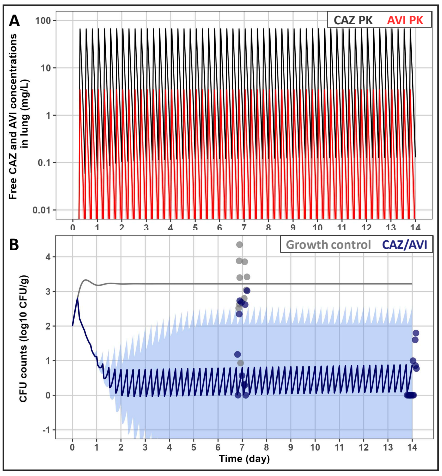


**Figure 3.** Lung PK and CFU predictions at 7 and 14 days
A. Free CAZ and AVI concentrations simulated in lung. B. Lung CFU predicted over time in infected rabbits treated with CAZ/AVI. Dots: lung CFU observed at 7 or 14 days in the growth control (grey) or CAZ/AVI treated group (blue). Line and shaded areas: median and the 95% confidence interval predicted by the model.

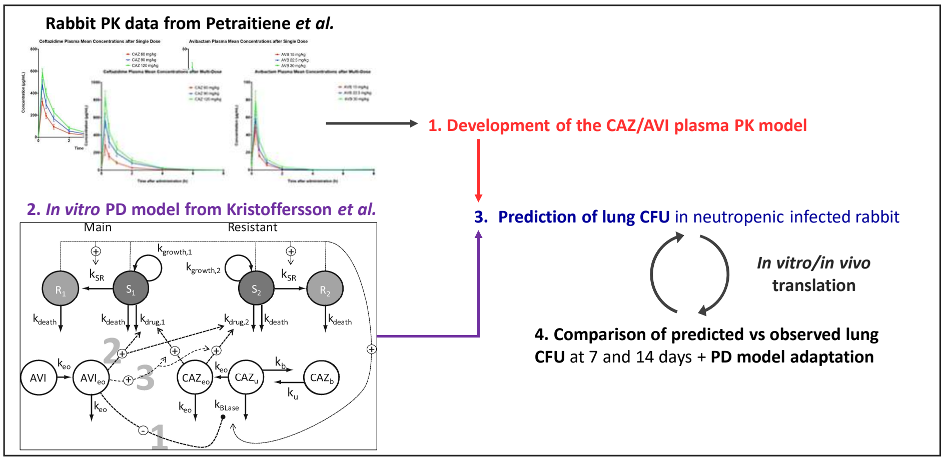


**Figure 1.** Workflow for model building and *in vitro/in vivo* translation

## Conclusion

- CAZ & AVI plasma PK in healthy rabbits were well described by **two-compartment PK models,** keeping the same model structure as in mouse (6) or human (7) and allowing further **interspecies PK translation**.
- Bacterial killing over time was overpredicted by the *in vitro* PD model and adaptation of PD parameters was required for translation to rabbits lung tissue. This study demonstrated that ***in vitro/in vivo* translation can be improved using PKPD modelling approach**.
- **After further adaptations**, the model will facilitate the characterization of *in vitro/in vivo* PKPD differences and strengthen **reliable preclinical to clinical translation** of antimicrobial drug effects.

In collaboration with

Weill Cornell Medicine
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