Emergence of ceftazidime resistant *Pseudomonas aeruginosa* during exposure to high concentrations of ceftazidime in vitro and in vivo

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Introduction and Purpose

- *Pseudomonas aeruginosa* exposed to ceftazidime *in vitro* can survive and become resistant, even when concentrations exceed the MIC during the entire dosing interval (T>MIC = 100%).
- Clinical studies have shown emergence of secondary resistance during ceftazidime treatment, but it is unclear whether this was related to the extent of exposure to ceftazidime.
- This study aimed to investigate the relationship between exposure to ceftazidime and emergence of resistant *P. aeruginosa* strains during ceftazidime treatment both *in vitro* and in critically ill patients.

Methods

- Development of resistance was followed *in vitro* in chemostat cultures of wild type strain *P. aeruginosa* ATCC27853 subjected to three ceftazidime doses producing concentration-time profiles modelling the 5, 50 and 95 percentiles of plasma concentrations after a 1000mg loading dose, followed by continuous infusion of 3000mg/24h.
- These profiles were simulated using non-linear mixed effects modelling (NONMEM) based on a population pharmacokinetic model for ceftazidime in critically ill patients published by Benko AS et al. (AAC 1996;40:691-5).
- The chemostat cultures were sampled every 24h for 7 days for cellular parameters and MIC measurements.
- In parallel, a prospective observational study was conducted in ICU patients treated with ceftazidime.
- Ceftazidime plasma concentrations were determined and clinical and surveillance cultures positive for *Pseudomonas aeruginosa* were collected for ceftazidime MIC measurement.
- Plasma concentrations were analyzed by NONMEM to calculate the exposure to ceftazidime, expressed as mean area under the plasma concentration-time curve (AUC_{0-24}) over the period of MIC change and as AUC_{0-72}.

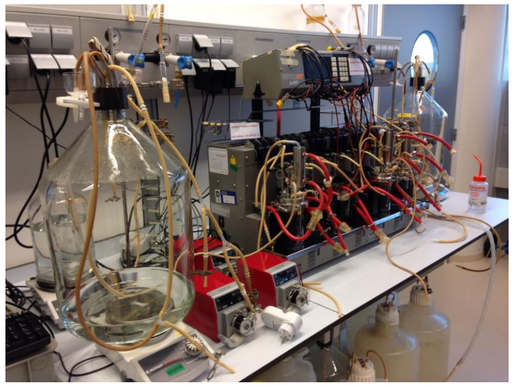


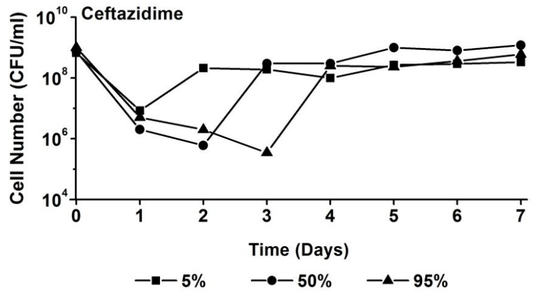
Figure 1. Chemostat used for in vitro experiments.

Results

- *In vitro*, the bacterial cell density of the culture decreased by a factor 100-10.000 within the first 3 days of simulated treatment and the MIC increased by 5-7 two-fold dilution steps (Figure 2).
- The most rapid increase occurred at the median concentration, the lowest concentration yielded a smaller and slower increase in MIC.
- The cells exposed to the highest concentration were the last to show an increased MIC, but the final MIC values were the highest.
- Thirty-nine ICU patients were included for the development of the population pharmacokinetic model. Consecutive *P. aeruginosa* isolates, separated by at least 72h, were available from 6 of these patients (Table 1).
- From one patient with a relatively high AUC_{0-72}, isolates showed an increase in MIC from 2 to >256 mg/L. For the other 5 patients, no change in MIC was observed.

Patient ID	ΔMIC (dilutions)	Mean AUC_{0-24} (mg*h/L)	AUC_{0-72} (mg*h/L)
1	1	128	1514
2a	1	111	445
2b	1	254	833
3	14	337	1485
4	0	680	1472
5	1	264	1056
6	1	247	972

Table 1. Changes in MIC and exposure to ceftazidime for patients with at least two positive cultures with Pseudomonas aeruginosa *separated by at least 72 hours.*



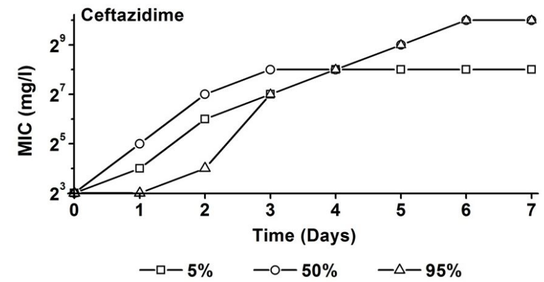


Figure 2. Bacterial cell densities and ceftazidime MICs of P. aeruginosa *in the chemostat during continuous infusion, simulating the 5, 50 and 95 percentiles of ceftazidime plasma concentrations in critically ill patients.*

Conclusions

- *In vitro*, the emergence of resistance to ceftazidime occurred within 3 days irrespective of dose.
- Although only a limited number of patients showed consecutive *P. aeruginosa* positive cultures, emergence of resistance during therapy was also observed in one patient.
- Inclusion of patients is still ongoing.