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Beta-lactam and quinolone pharmacokinetic/pharmacodynamic target attainment in critically ill patients (EXPAT)

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Background: The extreme pharmacokinetic (PK) behaviour of drugs sometimes observed in critically ill patients poses a significant threat to the achievement of optimal antibiotic treatment outcomes. Therapeutic drug monitoring (TDM) is a commonly used dosing strategy to optimize exposure and thereby minimize toxicity and maximize the efficacy. However, expansion of this practice to β-lactams and quinolones is not widely used as a routine intervention and data are still sparse as to whether individual patient variability would merit TDM for these two classes. The main objectives of this study are to (1) assess exposures of β-lactams and quinolones commonly use in critically ill patients in a routine ICU setting, and (2) whether the turnaround time of assays would justify TDM of these classes.

Material/methods: The EXPAT is an ongoing prospective, observational PK/PD study in 2 ICUs (teaching and academic hospital) in the Netherlands. We enrolled patients ≥18 years old administered frequently used β-lactams and quinolones, over a 6-month period. Based on optimal sampling, five separate 5-mL samples were taken at various time points. Plasma concentrations were determined by

a validated multi-analyte UPLC-MS/MS assay, with a simple and rapid preparation procedure and a total run-time of 5.20 minutes. The percentage ƒT>MIC were determined by calculating the intercept of the MIC values (0.5 to 8.0 mg/L) with the concentration-time curve. For the β-lactam antibiotics (cefotaxime, ceftriaxone), the primary PK/PD endpoints were the free concentrations above the minimum inhibitory concentration (MIC) at 100% (ICU target) of the dosing interval (100% ƒT>MIC and 100% ƒT>4xMIC). For the quinolones (ciprofloxacin), we determined the area under the free concentration time curve-to-MIC ratio (ƒAUC/MIC>100) and the maximum concentration of drug in serum-to-MIC ratio (ƒCmax/MIC>10). In the absence of cultures, the MIC values were derived from the EUCAST epidemiological cut-off (ECOFF) breakpoints.

Results: A total of 80 patients were included in this first interim analysis. The median age was 62 years, 60% of the patients were male, median APACHE II score was 23 and median creatinine clearance rate was 66 mL/min. All samples were assayed during routine lab procedures. Data describing the achievement of the PK/PD targets for the individual study antibiotics are shown in table 1. The 100% ƒT>MIC and 100% ƒT>4xMIC targets for MIC 4 mg/L (*Staphylococcus aureus* ECOFF) in the β-lactam patients were attained in 65% and 26%, respectively. The ƒAUC/MIC>100 and ƒCmax/MIC>10 targets for MIC 0.5 mg/L (*Pseudomonas aeruginosa* ECOFF) in the quinolone patients was attained in 38% and 19%, respectively.

Conclusions: The interim analysis at 6-months demonstrated that TDM of β-lactams and quinolones is feasible in a routine clinical setting. Empiric approaches to β-lactam and quinolones dosing in critically ill patients results in poor target attainment and would merit TDM for these agents.

Table 1 - Antibiotic PK/PD target attainment in ICU patients

	Cefotaxime 1g q6h n=35		**Cefotaxime 1g q4h** n=6		**Ceftriaxone 2g q24h** N=14		**Ciprofloxacin 400mg q12h** n=16		**Ciprofloxacin 400mg q8h** n=8	
MIC (mg/L)	100% ƒT>MIC	100% ƒT>4xMIC	100% ƒT>MIC	100% ƒT>4xMIC	100% ƒT>MIC	100% ƒT>4xMIC	ƒAUC/MIC ≥100	ƒCmax/MIC ≥10	ƒAUC/MIC ≥100	ƒCmax/MIC ≥10
0.5	97%	83%	83%	83%	100%	86%	25%	13%	50%	25%
1	97%	64%	83%	67%	100%	71%	6%	6%	13%	0%
2	78%	47%	83%	50%	86%	43%	0%	0%	0%	0%
4	58%	19%	67%	50%	71%	7%	0%	0%	0%	0%
8	39%	6%	50%	17%	36%	0%	0%	0%	0%	0%