β-lactam and fluoroquinolone pharmacokinetic/pharmacodynamic target attainment in critically ill patients (EXPAT)

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BACKGROUND

70%

EPIC II study (2009)
71% of the IC patients are treated with an antibiotic [1]

60%

Luyt et al. (2014)
30-60% of antibiotic prescriptions at the ICU are suboptimal [2]

60%

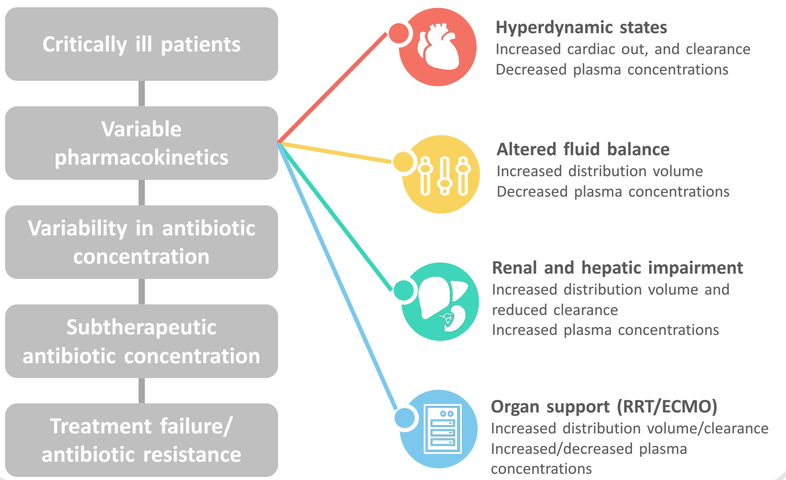
DALI study (2014)
60% of ICU patients receiving a β-lactams reaches 100% ƒT>MIC target [3]

30%

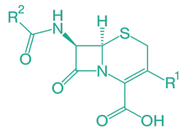
Van Zanten et al. (2008)
31% of ICU patients receiving ciprofloxacin 400 mg BID reaches AUC/MIC>125 target [4]

HYPOTHESIS

The effect of pathophysiological changes on pharmacokinetics in the critically ill patient



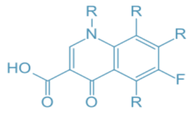
METHOD



β-lactam

amoxicillin, amoxicillin/clavulanic acid cefotaxime, ceftazidime, ceftriaxone, cefuroxime and meropenem

Pharmacokinetics	PK Target: ƒT>MIC
Hydrophilic Small volume of distribution Renal clearance 40-90%	Bacteriostase 40% ICU/severe infections 100%
Primary endpoints	**Secondary endpoints**
% ƒT>MIC 100% ƒT>MIC 100% ƒT>4xMIC	Disease severity scores: •T>MIC <100% vs 100% •T>4xMIC <100% vs 100%



Fluoroquinolones

ciprofloxacine

Pharmacokinetics	PK Target: ƒAUC/MIC
Hydrophilic Large volume of distribution Renal clearance 65%	Bacteriostase ≥40 ICU/severe infections ≥100
Primary endpoints	**Secondary endpoints**
ƒAUC/MIC % ƒAUC/MIC ≥100 % Cmax/MIC ≥10	Disease severity scores: •AUC/MIC <100 vs ≥100 •Cmax/MIC <10 vs ≥10

Study design
Two-center, prospective, observational pharmacokinetic and pharmacodynamic study, over a period of 18 months (interim analysis at 6 months)

Study population
ICU patients (+18 years) at the Erasmus MC and Maasstad Hospital, treated with frequently used β-lactam and fluoroquinolones

Objectives
To assess exposures of β-lactams and quinolones in a routine ICU setting, and whether the turnaround time of assays would justify TDM of these classes

Analysis
Bioanalysis: validated multi-analyte UPLC-MS/MS assay
Microbiology: MIC, EUCAST database
Data: PK data, NONMEM

AFFILIATIES
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ABBREVIATIONS
APACHE II: Acute Physiology and Chronic Health Evaluation II Score; **AUC** = Area Under the Curve; **AUC/MIC** = ratio AUC to the minimal inhibitory concentration; **Cmax** = Maximum Concentration; **Cmax/MIC** = ratio Maximum Concentration to minimal inhibitory concentration; **ECMO**: ExtraCorporeal Membrane Oxygenation; **EUCAST**: European Committee on Antimicrobial Susceptibility Testing; **NONMEM**: Non-linear Mixed Effect Modelling; **RRT**: Renal Replacement Therapy; **T** = Time; **UPLC-MS/MS**: Ultra-Performance Liquid Chromatography Tandem Mass-Spectrometry.

LITERATURE
1. Vincent JL, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302: 2323–9. **2.** Luyt, C.-E., et al., Antibiotic stewardship in the intensive care unit. Critical Care, 2014. 18(5): p. 480. **3.** Roberts JA, et al., : DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014, 58:1072–1083. **4.** van Zanten, A.R.H., et al., Ciprofloxacin pharmacokinetics in critically ill patients: A prospective cohort study. Journal of Critical Care, 2008. 23(3): p. 422-430.

RESULTS

80 patients

60% 40%

Median Age

62 year (24-85)

Apache II score

23 (7-38)

Median clearance

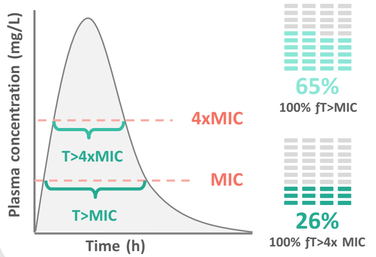
66 mL/min (24-85)

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%

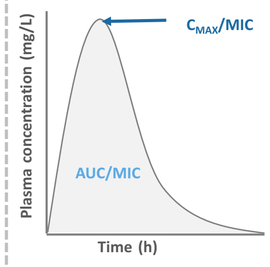
β-lactam Target Attainment

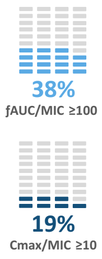
MIC of 4 mg/L (*S. aureus* epidemiological cut-off MIC)



Quinolones Target Attainment

MIC of 0.5 mg/L (*P. Aeruginosa* epidemiological cut-off MIC)





CONCLUSION

The interim analysis at 6-months demonstrated that empiric approaches to β-lactam and quinolones dosing in critically ill patients results in poor target attainment. Individualized dosing strategies in the ICU are necessary to optimize β-lactam and quinolones exposure. Our findings merit therapeutic drug monitoring for these agents.