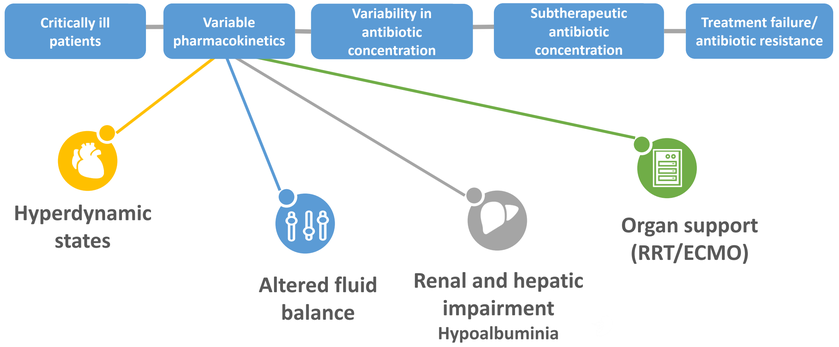
Large variability of unbound active fraction of **ceftriaxone** in contrast to **ciprofloxacin** in plasma of critically ill patients

Tim Ewoldt[1], Alan Abdulla[2], Diederik Gommers[1], Anouk Muller[3,4], Henrik Endeman[1], Birgit Koch[2]

BACKGROUND

The effect of pathophysiological changes on pharmacokinetics in the critically ill



METHODS

ICU patients, receive IV antibiotics, age ≥ 18 years, no burn-wounds, not pregnant

Samples were obtained from an ongoing multicentre RCT (DOLPHIN) at day 1, 3 and 5 after initiation of antibiotics

Total and unbound concentrations were measured using a validated UPLC-MS/MS method.

For predictors of free fraction, linear regression was used ($p<0.10$). These predictors were used in a multivariate regression ($p<0.05$). Data described as median [IQR]

RESULTS

38 patients | **137 samples** | **20 outliers removed** (+3SD)

Patient characteristics

	Ceftriaxone	Ciprofloxacin
Age (years)	66 [57,71]	74 [56, 77]
Length (cm)	174 [170,180]	175 [166,180]
Weight (kg)	92.0 [72.0,103]	75.0 [62.0,88.0]
Apache IV	89.0 [63.0,101]	66.0 [59.0,77.0]
Albumin (g/L)	26.0 [22.5,28.0]	25.0 [22.0,29.0]
Creatinine (umol/L)	125 [56.0,230]	102 [54.3,130]

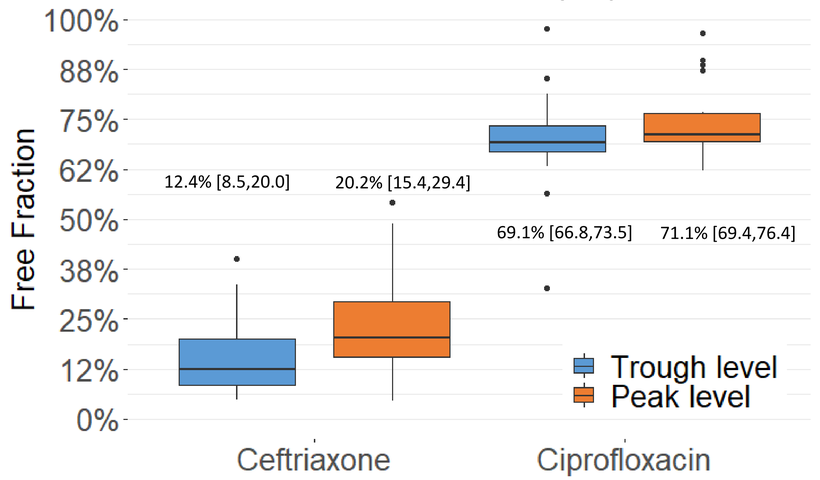
Prediction model of Ceftriaxone trough free fraction

	Estimate	P-value
Intercept	40.8%	0,001
Albumin (per g/L)	-0.76%	0,005
Creatinine (per umol/L)	0,3%	0,007
Age (per year)	-0,2%	0,17
Septic Shock	6,8%	0,01
Adjusted R^2	0,661	

Affiliations
1: Erasmus University Medical Center, Department of Intensive Care; **2**: Erasmus University Medical Center, Department of Hospital Pharmacy; **3**: Erasmus University Medical Center, Department of Medical Microbiology and Infectious Diseases; **4**: Haaglanden Medical Center, Department of Medical Microbiology

Abbrevations
ICU: Intensive care unit, **IV**: Intravenous, **RCT:** Randomised controlled trial, **UPLC-MS/MS:** Ultraperformance liquid chromatography with 2 mass spectrometers, **IQR:** Interquartile range

Antibiotic free fraction in critically ill patients



CONCLUSION

In contrast to the moderately and fairly constant bounded ciprofloxacin, the fraction of unbound concentration was extremely variable in ceftriaxone and especially for trough concentrations, higher than previously reported, resulting in fluctuations in effective exposure. At the moment unbound fraction is not considered when dosing ceftriaxone, but therapeutic drug monitoring unbound trough concentrations might increase the likelihood of therapeutic success.