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### High target attainment for B-lactam antibiotics in patients with Gram-negative blood stream infections when actual minimum inhibitory concentrations are applied

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# Conclusion

A higher target attainment was reached when using actual MIC values, compared to EUCAST breakpoints. Not attaining 100% fT > 4MIC was associated with significantly lower resolution of infection. Whether this has clinical importance needs further evaluation.

### Introduction

Beta-lactam antibiotics play an important role in the treatment of Gram-negative blood stream infections. The effect of betalactam antibiotics depends on the concentration above the minimal inhibitory concentration (MIC). The aim of this study was to investigate target attainment of 100% fT > MIC and of 100% fT > 4MIC when actual MIC values were applied compared to when using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.

### Methods

In this prospective single centre study, patients with Gramnegative blood stream infection ≥18 years old treated with cefotaxime, piperacillin/tazobactam or meropenem were included. Antibiotic concentrations were collected during a single dosing interval and actual MIC values were obtained. Target was set to free trough concentrations above MIC

during the entire dosing interval and four times above the MIC, meaning a pharmacokinetic pharmacodynamic (PK/PD) ratio of > 1 and > 4, respectively. Treatment response was defined as resolution (disappearance of initial infection under study after day 7 after initiation of antibiotic treatment) and non-resolution.

## Results

We included 100 patients with a median age of 72 years, 50% were females, median BMI was 27, median eGFR was 73

mL/min/1.73m<sup>2</sup> and median National Early Warning Score (NEWS) on admission was 5. Most common site of infection was urinary tract (52%) followed by abdominal (27%). Most common microbiological finding was *Escherichia coli* (62%) followed by *Klebsiella* (21%). Of all patients, 93/100 (93%) attained 100% fT > MIC and 77/100 patients (77%) attained 100% fT > 4MIC when actual MIC values were applied compared to 58/100 (58%) and 25/100 (25%) when EUCAST breakpoints were used. Achieving target of 100% fT > MIC was not associated with difference in resolution. Clinical resolution at day 7 was higher in patients attaining a target concentration of 100% fT > 4MIC, 49/77 (64%) compared to 100% *f*T < 4MIC, 9/23 (39%) (p=0.037).

Antibiotic data for pharmacokinetic/pharmacodynamic targets actual MIC

Dosing and PK/PD targets	Cefotaxime (n = 51)	Piperacillin (n = 30)	Meropenem (n = 19)	All (n=100)
100 % <i>f</i> T > MIC, no. (%)	50 (98)	24 (80)	19 (100)	93 (93)
100 % <i>f</i> T > 4MIC, no. (%)	44 (86)	14 (47)	19 (100)	77 (77)



PK/PD ratio by antibiotic and MIC values (clinical and EUCAST).







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MIC values per antibiotic in mg/L. The dots represent actual MIC values applied and the lines represent EUCAST MIC values.