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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.

Methods

In this prospective single centre study, patients with Gram-negative 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

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/1.73m² 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% $fT < 4MIC$, 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 % $fT > MIC$, no. (%)	50 (98)	24 (80)	19 (100)	93 (93)
100 % $fT > 4MIC$, no. (%)	44 (86)	14 (47)	19 (100)	77 (77)

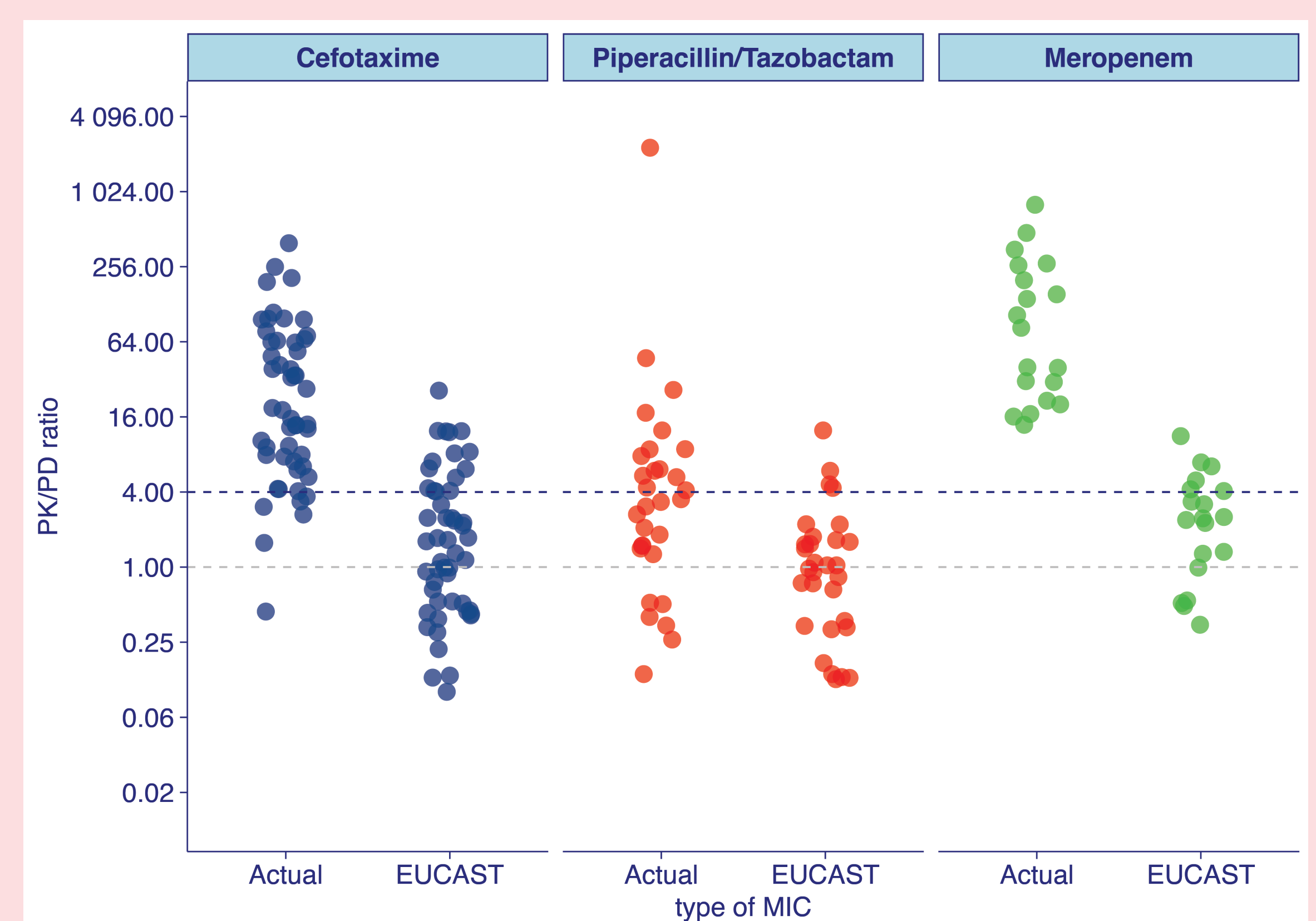
Antibiotic data for pharmacokinetic/pharmacodynamic targets EUCAST MIC

Dosing and PK/PD targets	Cefotaxime (n = 51)	Piperacillin (n = 30)	Meropenem (n = 19)	All (n=100)
100 % $fT > MIC$, no. (%)	29 (57)	15 (50)	14 (74)	58 (58)
100 % $fT > 4MIC$, no. (%)	15 (29)	4 (13)	6 (32)	25 (25)

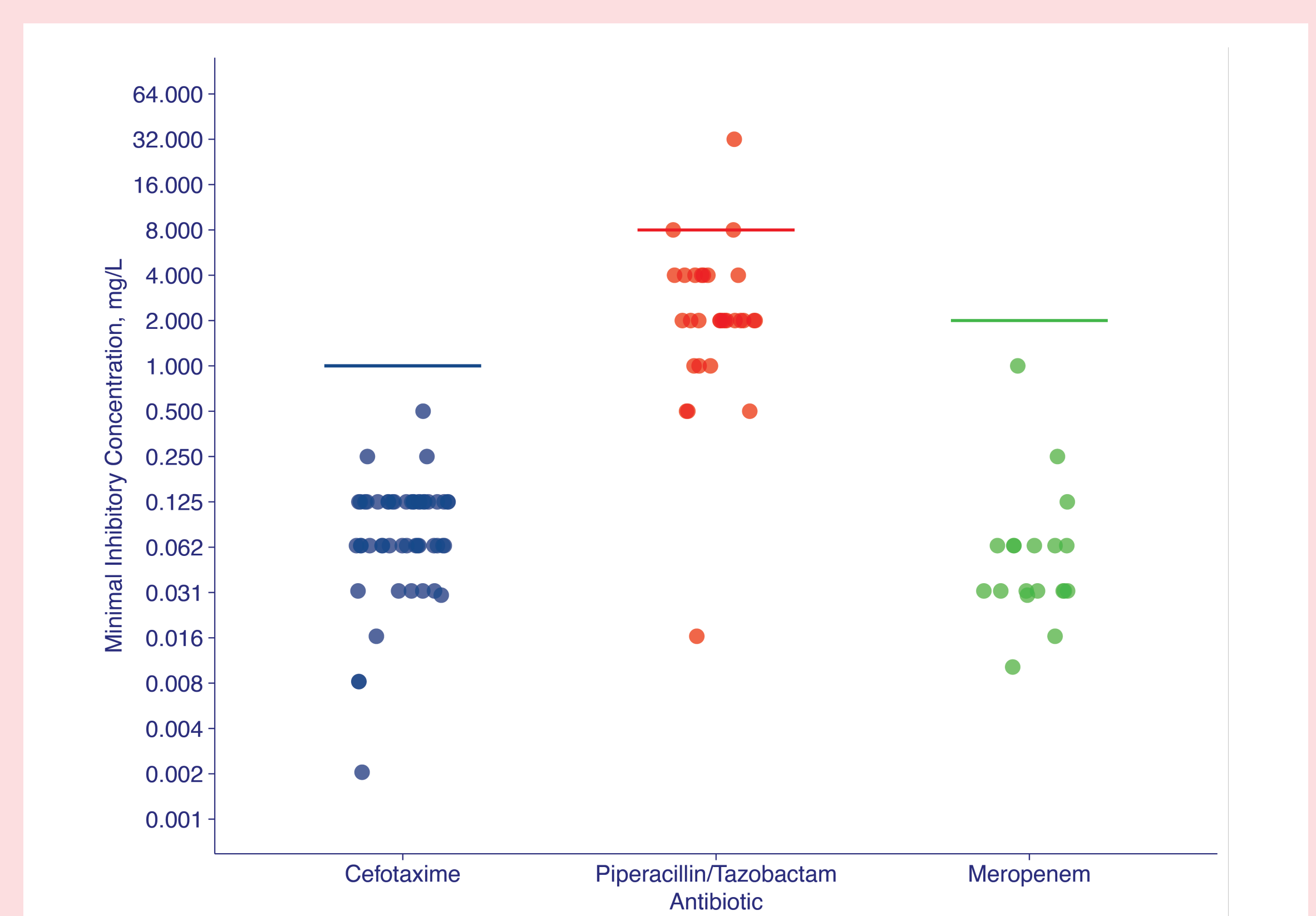
Introduction

Beta-lactam antibiotics play an important role in the treatment of Gram-negative blood stream infections. The effect of beta-lactam 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.

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.



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



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

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