Obesity and augmented renal clearance influence cefiderocol PK/PD target attainment in critically ill patients.

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Background

Cefiderocol is a β-lactam active against Gram-negative bacilli, including some metallo-betalactamases-producing Enterobacterales. Cefiderocol has been widely used in critically ill patients, but recommended dosages have not been extensively studied in real-life, clarifying how physio/pathological alterations may be associated with PK/PD abnormalities. A few data on morbidly/obese and augmented renal clearance (ARC) patients are present, making dose-adjustment recommendations only expected as expert opinion.

Methods

Patients with *K. pneumoniae* NDM infections were enrolled, treated with different cefiderocol regimens (3h infusion) and stratified based on BMI (Kg/m^2) as follow: healthy-weight (18.5-24.9); overweight (25-29.9); obesity (≥30). Plasma cefiderocol TDM was performed pre-, post-infusion, 1h-, 3h- and 5h-post-infusion. The conventional PK/PD target of *f*T>MIC has been considered, along with a more aggressive *f*T>6xMIC; evaluated clinical outcomes were microbiological eradication and 30-days mortality. ARC was defined as Cl_{cr}>130 mL/min (calculated with Cockrouft-Gault).

Results

Five patients were normal weight, two overweight and three obese (sub-analyses was performed comparing healthy-weight vs. non-healthy weight (overweight and obese). An association between body weight and mortality (p=0.038) was highlighted: three (60%) patients in the non-healthy weight group died at 30 days. Death was registered only in non-healthy weight group and in patients with BMI>30 (p=0.033). No patient from non-healthy weight group achieved pathogen eradication (p=0.010); conversely, 4 (80%) patients from healthy weight one reached the target; in detail, failure progressively increased with higher BMI (p=0.036).

All patients reached the conventional target of *f*Cmin>4 mg/L, while considering the more aggressive 100% *f*T>6xMIC (2 mg/L), two (40%) patients from non-healthy weight group reached 70%*f*T>6xMIC; these patients had ARC, with Cl_{cr}>180 mL/min. Augmented eGFR was associated with obesity (p=0.016) and a correlation between cefiderocol Cl and aggressive PK/PD target accomplishment was suggested (p=0.08).

Conclusions

Our data highlighted that BMI>30 negatively influence the probability of target attainment, increasing the risk of death and/or selecting resistance. It is worth noting that cefiderocol has manufacturer recommendation (2g, TID) for ARC, but indication is based on Cl_{cr} value not exceeding 130 mL/min. Based on our data, Cl_{cr} correlated with cefiderocol Cl, thus BMI- and Cl_{cr}-based dose adjustment, with TDM, should be evaluated to maximize therapeutic efficacy.

Key words: cefiderocol, PK/PD target, new β-lactam, critically ill patients, obesity, ARC