Evaluation of Safety of High-Dose Beta-Lactam Antibiotics in Patients with End-Stage Kidney Disease: A Retrospective Cohort Study

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Background

- β-lactam toxicity is often underestimated in clinical practice.[1]
- Cefepime, meropenem, and piperacillin-tazobactam are all renally cleared and have been associated with neurotoxicity and thrombocytopenia.[2]
- Renally impaired patients are at increased risk of toxicity due to drug accumulation.[3]
- This study's objective was to identify the rate of β-lactam-induced toxicities in patients with **end-stage kidney disease** (**ESKD**) on higher than recommended doses of piperacillin-tazobactam, cefepime, or meropenem compared to patients on appropriate doses.

Methods

- This retrospective cohort study included hospitalized patients 18 years and older with **ESKD** via ICD-10 code who received **piperacillin-tazobactam**, **cefepime**, or **meropenem** for at least 48 hours at Loma Linda University Medical Center from January 1, 2013 to June 30, 2021.
- Patients who received appropriate doses per package insert (cohort 1) were compared to those who received higher than recommended doses (cohort 2).
- The primary composite outcome of β-lactam toxicity consisted of **neurotoxicity**, **hepatotoxicity**, and **hematologic toxicity**.
- Multivariate logistic regression was done for variables with a p-value < 0.2 in bivariate analysis.

References

1. Imani S, et al. *J Antimicrob Chemother*. 2017;72(10):2891-2897.
2. Roger C, Louart B. *Microorganisms*. 2021;9(7):1505.
3. Maan G, et al. *J Antimicrob Chemother*. 2022;dkac271. [Online ahead of print]

Patients with ESKD on higher than recommended doses per package insert of piperacillin-tazobactam, cefepime, or meropenem for at least 48 hours were significantly at higher risk of β-lactam associated toxicity, specifically neurotoxicity.

Results

- Eligibility criteria were met by 341 patients, 193 in cohort 1 and 148 in cohort 2.
- The mean age in eligible patients was 58±15 years and 47% were female.
- Baseline characteristics were similar between cohort 1 and cohort 2 except for renal replacement therapy (82% vs 95%) and meropenem use (3% vs 9%).
- The mean duration of treatment was 7.3 days (7.0 vs 7.7).
- More patients experienced β-lactam toxicity in cohort 2:
  - **Any toxicity**: 59 vs 71%; OR **1.73 (1.07-2.81, *P*=0.02)**
  - **Neurotoxicity**: 29% vs 43%; OR **1.81 (1.13-2.92, *P*=0.01)**
  - Hepatotoxicity: 28% vs 37%; OR 1.52 (0.94-2.47, *P*=0.08)
  - Hematotoxicity: 28% vs 26%; OR 1.35 (0.82-2.20, *P*=0.23)
- Multivariate logistic regression identified age and receipt of higher than recommended doses as independent predictors for any toxicity (table) and neurotoxicity.

Variable	Bivariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.03 (1.01 to 1.04)	0.0006	**1.03 (1.01 to 1.04)**	**0.001**
Gender	0.98 (0.63 to 1.53)	0.94	-	-
Weight	1.01 (0.99 to 1.02)	0.29	-	-
BMI	1.01 (0.99 to 1.04)	0.28	-	-
RRT	1.18 (0.61 to 2.27)	0.61	-	-
IHD	1.19 (0.68 to 2.09)	0.53	-	-
PD	0.61 (0.25 to 1.50)	0.27	-	-
CRRT	2.30 (0.34 to 45.30)	0.46	-	-
Liver disease	1.44 (0.75 to 2.88)	0.28	-	-
Diabetes	0.97 (0.61 to 1.52)	0.89	-	-
Cefepime	0.92 (0.42 to 2.07)	0.83	-	-
Piperacillin-tazobactam	0.78 (0.40 to 1.48)	0.45	-	-
Meropenem	2.20 (0.78 to 7.85)	0.17	1.31 (0.43 to 4.91)	0.65
Duration of abx therapy	1.04 (1.00 to 1.09)	0.05	1.03 (0.99 to 1.08)	0.10
Overdose	1.73 (1.10 to 2.74)	0.02	**1.63 (1.02 to 2.63)**	**0.04**

BMI, body mass index; RRT, renal replacement therapy; IHD, intermittent hemodialysis; PD, peritoneal dialysis; CRRT, continuous renal replacement therapy; abx, antibiotic