Patients with Piperacillin/Tazobactam-Associated Acute Kidney Injury Have Higher Piperacillin Exposures

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INTRODUCTION

Purpose of Antibiotic Precision Dosing: Ensure Attainment of Antibiotic Targets and Reduce Toxicity

- Model-informed precision dosing uses population pharmacokinetic (PK) models, individual patient factors and measured concentrations ([ ]) to maximize bactericidal activity and minimize toxicity

Piperacillin/Tazobactam is an Ideal Candidate for Precision Dosing

- Piperacillin/Tazobactam (PTZ) is frequently used in critically ill children for infections and is associated with nephrotoxicity
- Knowledge gap:
  - Relationship between [piperacillin] and PTZ-associated acute kidney injury (AKI) development is uncertain
- **Determining [piperacillin] thresholds and clinical factors associated with PTZ-AKI is a critical step for PTZ precision dosing**

OBJECTIVE

Assess the relationship between [piperacillin] and PTZ-AKI and identify [piperacillin] thresholds associated with PTZ-AKI

METHODS AND MATERIALS

Use of an Existing Dataset of [Piperacillin] Collected by Opportunistic Sampling

- 149 critically ill patients administered ≥1 PTZ dose
- Free [piperacillin] were measured using HPLC
- Exclusion criteria
  - Received PTZ for <24 hours or doses at another institution
  - On extracorporeal life support devices: CRRT, ECMO, MARS

Piperacillin Exposure Measurements

Using Bayesian estimation, a published piperacillin population PK model (de Cock, 2015) and measured [piperacillin], the precision dosing clinical software MWPharm++ (Mediware, Czech Republic) can estimate AUC, highest C_{max}, highest C_{min} in first 24 hours (Figure 1)

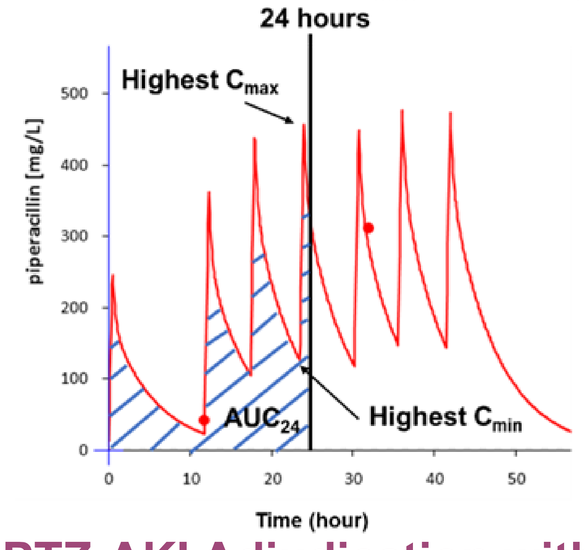

Figure 1: Simulated piperacillin concentration vs. time curve for a patient with measured piperacillin concentrations (red circles) to demonstrate highest maximum piperacillin concentration (C_{max}) and minimum piperacillin concentration (C_{min}) and area under the curve (AUC_{24}) in the first 24 hours.

PTZ-AKI Adjudication with Naranjo Adverse Drug Reaction Probability Scoring

- PTZ- AKI definition (meet first 2 or all 3 criteria)
  1. AKI present >24 hours after exposure to 1st PTZ dose and
  2. AKI meets KDIGO stage 2 criteria or higher and
  3. Increase in Cr is at least above 0.5 mg/dL
- 3 Physician Adjudicators determined presence of PTZ-AKI and likelihood of AKI using the Naranjo Adverse Drug Reaction Probability Scale in RedCap
- Probability scale: Unlikely, Possible, Probable, Definite

RedCap Form

Statistical Analysis: compared patients with and without PTZ-AKI: t-test of log-transformed piperacillin exposure measurements

RESULTS

107 of 149 Patients Included in Final Cohort; 15% met 3 PTZ-AKI criteria and rated as possible or probable likelihood

PTZ- AKI Adjudication Decision	Number of Patients (%)
No	67 (62.6)
Unlikely	3 (2.8)
Possible	35 (32.7)
Meets all 2 criteria	20 (18.7)
Meets first 3 criteria	15 (14.0)
Probable	2 (1.8)
Meets all 2 criteria	1 (0.9)
Meets first 3 criteria	1 (0.9)

Patients with PTZ-AKI are older, have higher weights

	Overall (N=107)	PTZ-AKI (N=16)	No PTZ-AKI (N=91)	p-value
Age (years)				**<0.001**
Median [IQR]	6.28 [2.2, 12.8]	14.8 [11.8, 17.9]	5.36 [1.63, 11.0]	
Weight (kilograms)				**<0.001**
Median [IQR]	21.7 [11.5, 12.8]	44.7 [28.4, 58.3]	17.7 [10.9, 27.3]	
Baseline Creatinine Clearance (Bedside Schwartz Equation, mL/min/1.73m²)				0.091
Median [IQR]	219 [146, 262]	166 [138, 202]	199 [148, 268]	

Patients with PTZ-AKI: Higher Piperacillin Area Under the Curve and Troughs in first 24 hours

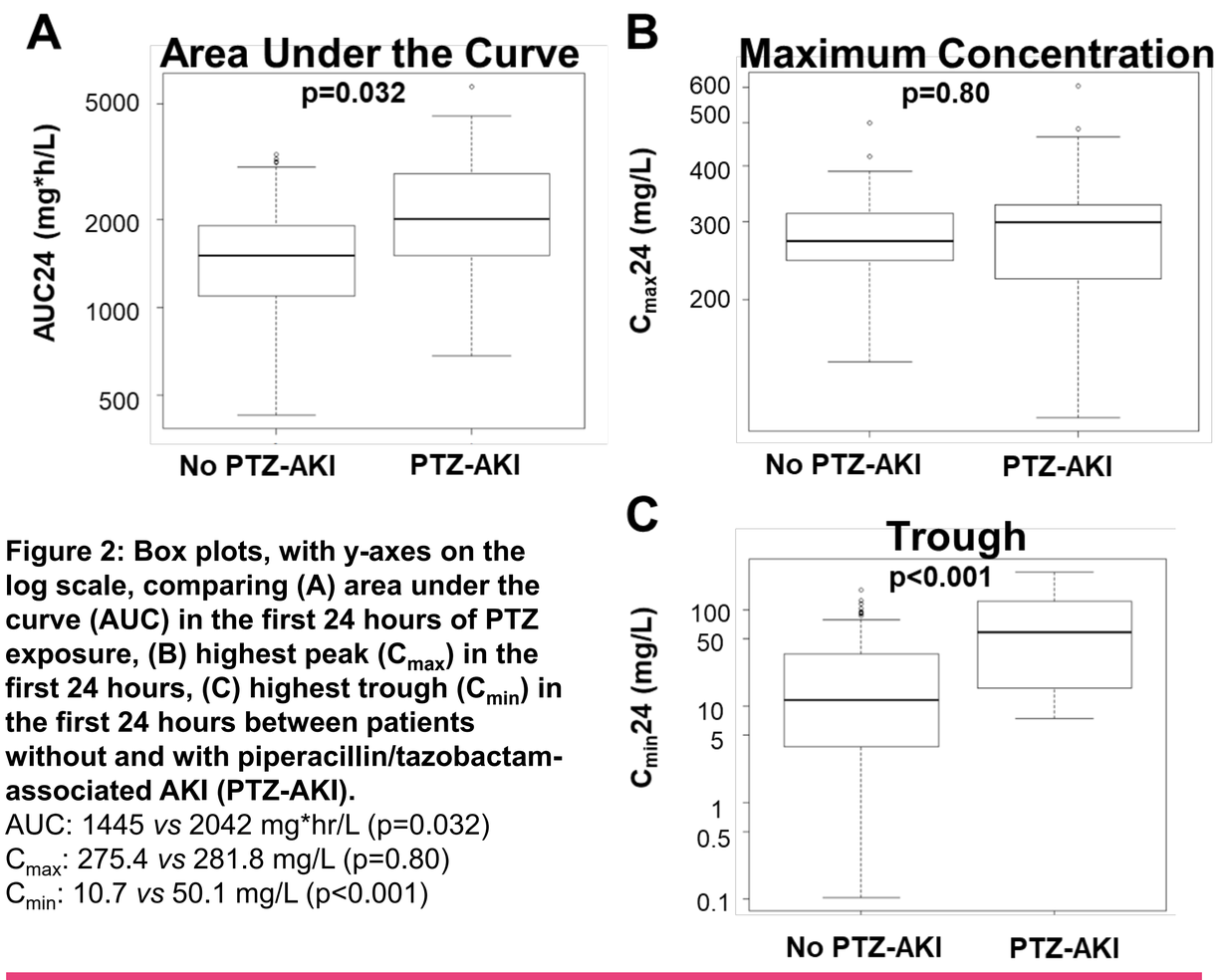

Figure 2: Box plots, with y-axes on the log scale, comparing (A) area under the curve (AUC) in the first 24 hours of PTZ exposure, (B) highest peak (C_{max}) in the first 24 hours, (C) highest trough (C_{min}) in the first 24 hours between patients without and with piperacillin/tazobactam-associated AKI (PTZ-AKI).

AUC: 1445 *vs* 2042 mg*hr/L (p=0.032)
C_{max}: 275.4 *vs* 281.8 mg/L (p=0.80)
C_{min}: 10.7 *vs* 50.1 mg/L (p<0.001)

CONCLUSIONS

- We developed a robust adjudication process to determine PTZ-AKI
- We show a relationship between piperacillin AUC and Cmin in first 24 hours of PTZ-therapy and PTZ-AKI development
- Older age is associated with PTZ-AKI development
- Multivariable logistic regression will be conducted to identify other predictors of PTZ-AKI
- These data could serve as the foundation for PTZ precision dosing to reduce PTZ-AKI

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