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Risk Factors for Infection or Colonization with Piperacillin-Tazobactam (TZP) Resistant *P. aeruginosa* with increasing degrees of β-lactam Resistance

angievit@umich.edu
586-303-6649

Angelina Jessica Vita[1], Seth Rice, PharmD[1], Owen Albin, MD[2], Twisha S. Patel, PharmD[1], Charles N. Styron, PharmD[1], Keith S. Kaye, MD, MPH[3], Jason M. Pogue, PharmD[1]
University of Michigan College of Pharmacy, Ann Arbor, MI[1]
Department of Medicine, Michigan Medicine, Ann Arbor, MI[2]
Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ[3]

Background

- *Pseudomonas aeruginosa* (PSA) is a leading cause of nosocomial infection with the CDC estimating 51,000 cases caused by multi-drug resistant (MDR) strains per year in the United States.
- The presence of MDR in PSA results in delays in time to appropriate therapy, longer hospital stay, increased risk of mortality, and rising healthcare costs.
- Rapid diagnostics can identify PSA, but as resistance to anti-pseudomonal β-lactams is most commonly due to mutations of chromosomal mechanisms, little is gleaned with regards to susceptibility.
- While risk factors for piperacillin-tazobactam (TZP) resistance in PSA have been identified and can be applied at the time of organism identification, co-resistance amongst traditional agents is common, making treatment decisions challenging.

Objective

Identify unique predictors for increasing degrees of beta-lactam resistance amongst piperacillin-tazobactam-resistant PSA.

Methods

- Retrospective, single-center, case-case-case-control study from September 2015 to June 2021
- Inclusion criteria: ≥ 18 years of age, admission to Michigan Medicine, and a clinical culture positive for PSA
- Exclusion criteria: patients with cystic fibrosis

Group	Definition
Control	Susceptibility to TZP
TZP-R ONLY	Nonsusceptibility to TZP but susceptible to cefepime, ceftazidime, and meropenem
TZP-R PLUS	Nonsusceptibility to piperacillin-tazobactam and 1 or 2 additional beta-lactams
PBR	Nonsusceptibility to TZP, cefepime, ceftazidime, and meropenem

- Patients with multiple positive isolates over the study period were categorized based on their most-resistant phenotype. Each patient was only included in the cohort once.
- Demographics, comorbidities, microbiologic, antibiotic, and healthcare exposures were assessed as potential predictors in each case-control model.
- Bivariate modeling was first performed for each case-control model. Variables with a p-value of 0.1 or less in the bivariate analysis were eligible for inclusion in the multivariate model.
- Logistic regression was then performed, and variables with p values < 0.05 were considered statistically significant. Independent predictors of each resistance phenotype were assessed.
- The three case-control models were then qualitatively compared to identify unique predictors for different degrees of resistance.

Results

Select Bivariate Analysis

Microbiologic Histories in past 90 days

Variables	Control (n=1954)	TZP-R ONLY (n=113)	P-value	TZP-R PLUS (n=179)	P-value	PBR (n=119)	P-value
PSA	168 (9%)	15 (13%)	0.1	**36 (20%)**	**<0.001**	**37 (31%)**	**<0.001**
TZP-R PSA*	12 (0.6%)	2 (2%)	0.18	**20 (11%)**	**<0.001**	**22 (18.5%)**	**<0.001**
PBR PSA**	0	0	1	0	1	**9 (8%)**	**<0.001**

*TZP-R PSA = piperacillin-tazobactam resistant PSA
** PBR PSA = pan β-lactam resistant PSA (resistant to TZP, cefepime, ceftazidime, meropenem)

Select Antibiotic Use in past 90 days

Variables	Control (n=1954)	TZP-R ONLY (n=113)	P-value	TZP-R PLUS (n=179)	P-value	PBR (n=119)	P-value
Piperacillin Tazobactam	449 (23%)	34 (30%)	0.09	**71 (40%)**	**<0.001**	35 (29.4%)	0.12
Ceftriaxone or Cefotaxime	79 (4%)	**17 (15%)**	**<0.001**	**15 (8.4%)**	**0.012**	4 (3.4%)	1
Cefepime	275 (14%)	**30 (26.5%)**	**<0.001**	**52 (29%)**	**<0.001**	**37 (31%)**	**<0.001**
Aztreonam	39 (2%)	1 (1%)	0.7	10 (6%)	0.006	3 (2.5%)	0.73
Fluoroquinolones	93 (5%)	10 (9%)	0.07	15 (8.4%)	**0.048**	**20 (17%)**	**<0.001**
Carbapenems	48 (2.5%)	5 (4.5%)	0.21	16 (9%)	**<0.001**	**33 (28%)**	**<0.001**

Multivariate Analysis —Comparison to Control

Variables	TZP-R ONLY	TZP-R PLUS	PBR
Ceftriaxone or Cefotaxime	**3.35 (1.86 – 6.02)**		
Cefepime	1.58 (0.99 – 2.54)	**1.87 (1.20 – 2.79)**	**1.64 (1.02 – 2.66)**
TZP		**2.17 (1.45 – 3.25)**	
Aztreonam		**2.38 (1.05 – 5.39)**	
Carbapenems			**7.58 (4.24 – 13.56)**
P. aeruginosa in previous 90 days	1.53 (0.84 – 2.90)	0.97 (0.54 – 1.74)	1.84 (0.99 – 3.42)
TZP-R PSA in previous 90 days		**18.0 (6.93 – 46.77)**	**13.19 (4.76 – 36.55)**
Isolation >48 hours after admission	1.27 (0.80 – 2.0)	**1.46 (1.01 – 2.10)**	
Recent ICU admission		**1.66 (1.03 – 2.68)**	
Skilled nursing facility transfer			**2.72 (1.09 – 6.83)**
Respiratory site of isolation			**1.64 (1.01 – 2.66)**
Presence of indwelling device			**1.70 (1.10 – 2.63)**
Hemiplegia or Paraplegia			**2.21 (1.33 – 3.68)**

Discussion

- Use of ceftriaxone or cefotaxime in the past 90 days was the only independent predictor specific to the TZP-R ONLY phenotype.
- Previously identified risk factors predicting for TZP-R PSA (e.g., previous antibiotic use and history of resistant *P. aeruginosa*) are not specific for TZP-resistance and are, in reality, predictors of greater degrees of resistance to traditional anti-pseudomonal β-lactams.
- Notable predictors include history of TZP-R PSA in the previous 90 days for TZP-R PLUS and PBR and carbapenem use in the last 90 days for PBR isolates.
- These data suggest that if concern for piperacillin-tazobactam resistance in PSA is present based on risk factors, that escalation to other traditional anti-pseudomonal β-lactams would offer no benefit, and alternate strategies need to be considered.