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Acute Kidney Injury in Patients with Pneumonia on Concomitant Anti-Methicillin Resistant *Staphylococcus aureus* and Anti-Pseudomonal Beta-Lactam Therapy

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REVISED ABSTRACT

Background: Empiric antibiotic treatment of serious and healthcare associated pneumonia (PNA) often includes coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (PSA). Recent publications suggest that patients treated with the combination of vancomycin (V) and piperacillin-tazobactam (PT) have a greater risk of acute kidney injury (AKI) than those treated with V alone, or V in combination with another β-lactam, such as cefepime (C). There is a paucity of data regarding the risk of AKI in other regimens that provide MRSA and PSA coverage, such as linezolid (L)-PT or LC. We examined the incidence of nephrotoxicity in patients who received combination antibiotic therapy for PNA.

Methods: A retrospective cohort analysis of eligible adult patients (≥ 18 years) admitted from July 1, 2014 to June 30, 2017 who received ≥ 48 hrs of combination therapy was conducted. Patients were excluded if their baseline serum creatinine was ≥ 1.4 mg/dL, on renal replacement therapy, or if diagnosed with cystic fibrosis. The primary outcome was incidence of AKI as defined by RIFLE criteria. Comparisons between the groups were analyzed by Chi-Squared test. To identify variables associated with AKI in a multivariable analysis, a repeated measures, mixed-effects logistic regression was utilized.

Results: There were 185 patient encounters included in the analysis. RIFLE-defined AKI occurred in treatment groups as follows: VPT 31/98 (31.6%); VC 5/50 (10.0%); LPT 4/12 (33.3%); and LC 4/25 (16.0%). There was a significant difference in rates of AKI among the 4 groups (*P*=.019). In pooled analyses, no difference was identified between patients receiving V or L (*P*=.73); however, patients who received PT had a higher incidence of AKI compared to those that received C (*P*=.002). In logistic regression analyses, independent predictors of AKI were receipt of PT vs C (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.3-8.0) and SOFA score ≥ 9 (OR, 4.5; 95% CI 1.6-12.7).

Conclusions: No differences in AKI incidence were found between patients receiving vancomycin or linezolid; however, patients receiving piperacillin-tazobactam and those with SOFA scores ≥9 had a higher rate of AKI.

INTRODUCTION

Empiric antibiotic selection for treatment of serious and healthcare associated infections, such as pneumonia, often includes coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.

Recent literature proposes that patients treated with the combination of vancomycin and piperacillin-tazobactam have a greater risk of AKI than those treated with vancomycin monotherapy or vancomycin in combination with another β-lactam, such as cefepime.

There is a paucity of data regarding the risk of AKI with other regimens that provide coverage of MRSA and *P. aeruginosa*, such as linezolid plus piperacillin-tazobactam or linezolid plus cefepime.

METHODS

Inclusion Criteria

- Hospitalized patients (≥ 18 years) with ICD-9/ICD-10 code for pneumonia
- Received concomitant anti-MRSA and anti-Pseudomonal therapies for ≥ 48 hours. Both agents were initiated within 24 hours of each other
  - Vancomycin + Piperacillin-Tazobactam (VPT)
  - Vancomycin + Cefepime (VC)
  - Linezolid + Piperacillin-Tazobactam (LPT)
  - Linezolid + Cefepime (LC)
- July 1, 2014 to June 30, 2017

Exclusion Criteria

- Baseline serum creatinine ≥ 1.4 mg/dL
- Baseline serum creatinine collected ≥ 24 hours after therapy initiation
- No additional serum creatinine values
- Receiving renal replacement therapy at therapy initiation
- Cystic fibrosis

Primary Objective

- To determine the rate of RIFLE-defined AKI in patients receiving VPT, VC, LPT, and LC at our institution

Secondary Objectives

- To compare rates of AKI in patients treated with the 4 different therapies
- To characterize the timing of AKI in patients treated for pneumonia with combination therapy
- To identify other risk factors for AKI in patients treated for pneumonia with combination therapy
- To characterize clinical outcomes such as mortality rate and length of stay

Study Design

- Retrospective cohort study. Patients were first divided into 4 groups based on which combination therapy they received
- Patients that experienced an AKI were compared with those that did not
  - Categorical and continuous data were compared using chi-square test two-sample t-test, respectively
  - Factors associated with AKI were assessed using Wilcoxon rank-sum test. In a multivariable analysis, a repeated measures, mixed-effects logistic regression was utilized

RESULTS

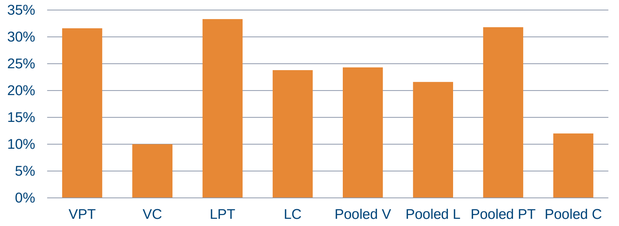
- 693 patient encounters were assessed for eligibility
- 185 patient encounters met inclusion criteria

Table 1. Baseline Characteristics by Combination Therapy Group

Characteristic	VPT (n = 98)	VC (n = 50)	LPT (n = 12)	LC (n = 25)
Age, y, mean (SD)	56.9 (16.5)	61.2 (15.3)	43.2 (13.4)	56.7 (15.1)
SOFA Score ≥ 9	8 (8.2)	5 (10.0)	2 (16.7)	1 (4.0)
ICU Admission	32 (32.7)	15 (30.0)	6 (50.0)	6 (24.0)
Baseline Creatinine Clearance, median (IQR)	69.8 (49.0-91.0)	62.9 (45.9-91.4)	92.9 (85.0-108.8)	65.9 (52.7-96.1)
≥ 1 Concomitant Nephrotoxin	67 (68.4)	33 (66.0)	8 (66.7)	17 (68.0)

Data are presented as number (%) unless otherwise specified

Figure 1. Rate of AKI



- Comparisons between the following groups were statistically significant
  - VPT vs VC (*P* = .004)
  - LPT vs VC (*P* = .04)
  - Pooled PT vs Pooled C (*P* = .002)

Figure 2. Pooled Time-to-AKI Comparison

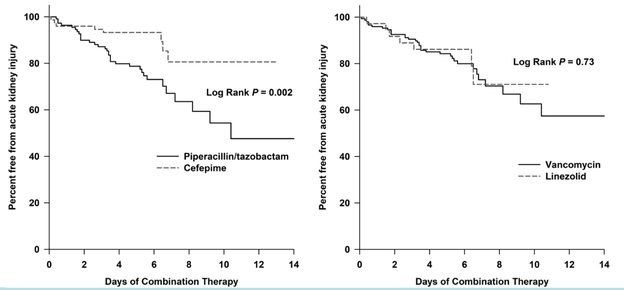


Table 2. Factors Associated with AKI

Factor	AKI (n = 44)	No AKI (n = 141)	*P* value
Age, y, mean (SD)	54.4 (15.4)	58 (16.4)	.19
Female	25 (56.8)	82.0 (58.2)	.88
Race			
Caucasian	12 (27.3)	52 (36.9)	.24
Black/African American	30 (68.2)	86 (61.0)	.39
Length of stay, d, median (IQR)	15.5 (8-27.5)	9 (6-14)	<.001
Charlson Comorbidity Index, median (IQR)	4.8 (2.0-7.0)	3.2 (2.0-6.0)	.61
SOFA Score ≥ 9	13 (30.0)	11 (7.8)	<.001
SOFA Score, median (IQR)	4.5 (2.0-9.0)	3.0 (1.0-5.0)	.002
ICU Admission	22 (50.0)	37 (26.2)	.003
Mortality	4 (9.1)	11 (7.8)	.78
Receipt of piperacillin-tazobactam	35 (79.5)	75 (53.2)	.002
Concomitant Nephrotoxins			
Acyclovir	3 (6.8)	0	.013
Aminoglycoside	0	4 (2.8)	.57
ACEi	3 (6.8)	19 (13.5)	.29
ARB	2 (4.5)	8 (5.7)	1.00
Diuretic	23 (52.3)	37 (26.2)	.002
IV Contrast	16 (36.4)	45 (31.9)	.58
Vasopressor	9 (20.5)	15 (10.6)	.12

ACEI – Angiotensin Converting Enzyme inhibitor
ARB – Angiotensin Receptor Blocker

Data are presented as number (%) unless otherwise specified

- Factors independently associated with AKI after controlling for differences
  - Receipt of piperacillin-tazobactam: OR = 3.15; 95% CI 1.25-7.95; *P* =.019
  - SOFA score ≥ 9: OR = 4.46; 95% CI 1.57-12.72; *P* =.009

CONCLUSIONS

- Combination treatment for pneumonia that included piperacillin-tazobactam was associated with increased odds of developing an AKI
- The substitution of linezolid for vancomycin did not abate this risk
- Patients treated with piperacillin-tazobactam experienced AKI more rapidly than those treated with cefepime
- The expansion of stewardship activities in patients on broad spectrum antimicrobials for pneumonia could lead to identification of patients in whom treatment with these combinations may not be a necessity

REFERENCES

1. Navalkele B, Pogue JM, Karino S, Nishan B, Salim M, Solanki S, et al. Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin-Tazobactam Compared to Those on Vancomycin and Cefepime. Clin Infect Dis. 2017;64(2):116-23.