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# Acute Kidney Injury in Patients Treated with Beta-lactam/Beta-lactamase Inhibitor Combinations

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## Abstract

**Background**: Recent literature has implicated the combination of piperacillin-tazobactam (PTZ) and vancomycin (VAN) in increasing incidence of acute kidney injury (AKI) compared to other combinations. The mechanism of this interaction is unknown, but may be due to the administration of a beta-lactamase inhibitor concomitantly. This study evaluated the difference in AKI rate among patients treated with ampicillin-sulbactam (SAM) compared to those receiving PTZ.

**Methods**: Clinical data from 9/1/2007 through 9/30/2015 were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust. Patients receiving SAM or PTZ for >48 hours were included. Patients were matched on: Charlson Comorbidity Index (CCI), baseline creatinine clearance, hypotension exposure, various nephrotoxic drug exposures, diagnosis of diabetes, heart failure, and hypertension. Basic descriptive statistics and multivariate regression were performed.

**Results**: Overall, 13,592 patient encounters were evaluated, with 612 and 12,980 receiving SAM and PTZ, respectively. On average, the PTZ group was slightly older (54 ± 17 vs 52 ± 15 years, p=0.0003), slightly less ill (CCI 3 [1-7] v 5 [2-9], p<0.00001), and had worse baseline creatinine clearance (91 [66-120] v 100 [78-128] mL/min, p<0.0001). AKI occurred in 2,934 (21.6%) patients in total, with 9.2% and 22.2% of SAM and PTZ patients experiencing AKI, respectively (p<0.00001). SAM patients were matched to 1,836 PTZ patients. In the matched cohort, 9.2% and 11.4% of SAM and PTZ patients experienced AKI, respectively (p=0.14). However, when VAN exposure is considered, the AKI rates are 8.9% SAM, 10.2% SAM+VAN, 9.5% PTZ, and 18.1% PTZ+VAN. After multivariate regression, receipt of PTZ+VAN was associated with an adjusted OR of 1.97 (95% CI 1.41-2.73, p <0.001) compared to PTZ alone. Whereas, receipt of SAM (p=0.5) or SAM+VAN (p=0.6) were not associated with increased odds of AKI.

**Conclusions**: AKI incidence was similar in patients treated with SAM and PTZ; however, the addition of VAN to PTZ significantly increased AKI incidence. This study demonstrates that the administration of multiple beta-lactam agents is not the likely mechanism for increased AKI observed with PTZ and VAN.

## Background

- Piperacillin-tazobactam (PTZ) is a beta-lactam/beta-lactamase inhibitor combination associated with increased rates of acute kidney injury (AKI) in patients receiving vancomycin (VAN) therapy
- Previous studies have compared PTZ to agents such as cefepime, which only contain one beta-lactam agent
- The coadministration of piperacillin with tazobactam may play a role in increasing AKI rates

## Objective

- Evaluate the difference in AKI rate among patients treated with ampicillin-sulbactam (SAM) compared to those receiving PTZ

## Results

**Table 1: Baseline patient characteristics (unmatched and matched cohorts)**

| Variable | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| | SAM (N=612) | PTZ (N=12,980) | p | SAM (N=612) | PTZ (N=1,836) | p |
| Age (median [IQR]) | 52 (42-62) | 55 (43-66) | **0.0003** | 52 (42-62) | 53 (40-63) | 0.7 |
| Gender | | | 0.7 | | | 0.2 |
| Male | 338 (55.2%) | 7,292 (56.2%) | | 338 (55.2%) | 954 (52.0%) | |
| Female | 274 (44.8%) | 5,688 (43.8%) | | 274 (44.8%) | 882 (48.0%) | |
| Caucasian | 554 (90.5%) | 11,624 (89.6%) | 0.5 | 554 (90.5%) | 1,648 (89.8%) | 0.6 |
| Weight (mean[SD]) | 79.9 (22.4) | 82.9 (24.2) | 0.2 | 79.9 (22.4) | 80.5 (23.8) | 0.8 |
| BMI (mean[SD]) | 27.7 (7.0) | 28.4 (11.0) | 0.3 | 27.7 (7.0) | 27.8 (8.8) | 0.9 |
| Charlson Score (median [IQR]) | 5 (2-9) | 3 (1-7) | **<0.00001** | 5 (2-9) | 4 (1-9) | **0.002** |
| Baseline CrCl (median [IQR]) | 100 (77.8-127.5) | 90.9 (65.6-120.7) | **<0.00001** | 100 (77.8-127.5) | 103.9 (76.8-130.9) | 0.4 |
| Baseline CrCl group | | | **<0.00001** | | | 0.8 |
| 30-59 mL/min | 64 (10.5%) | 2,512 (19.4%) | | 64 (10.5%) | 181 (9.9%) | |
| 60-89 mL/min | 165 (27.0%) | 3,862 (29.8%) | | 165 (27.0%) | 482 (26.3%) | |
| >=90 mL/min | 383 (62.6%) | 6,606 (50.9%) | | 383 (62.6%) | 1,173 (63.9%) | |
| Hypotension | 42 (6.9%) | 6,010 (46.3%) | **<0.00001** | 42 (6.9%) | 144 (7.8%) | 0.5 |
| Concomitant nephrotoxins | | | | | | |
| Aminoglycoside | 17 (2.8%) | 1,665 (12.8%) | **<0.00001** | 17 (2.8%) | 36 (2.0%) | 0.3 |
| Amphotericin B | 1 (0.2%) | 151 (1.2%) | **0.04** | 1 (0.2%) | 3 (0.2%) | 1 |
| ACE inhibitor | 88 (14.4%) | 2,449 (18.9%) | **0.006** | 88 (14.4%) | 217 (11.8%) | 0.1 |
| ARB | 25 (4.1%) | 437 (3.4%) | 0.4 | 25 (4.1%) | 59 (3.2%) | 0.4 |
| Contrast | 20 (3.3%) | 650 (5.0%) | **0.06** | 20 (3.3%) | 107 (5.8%) | **0.02** |
| Loop diuretic | 92 (15.0%) | 4,051 (31.2%) | **<0.00001** | 92 (15.0%) | 242 (13.2%) | 0.3 |
| NSAID | 106 (17.2%) | 1,941 (15.0%) | 0.1 | 106 (17.2%) | 294 (16.0%) | 0.5 |
| Calcineurin inhibitor | 21 (3.4%) | 497 (3.8%) | 0.7 | 21 (3.4%) | 57 (3.1%) | 0.8 |
| Vancomycin | 128 (20.9%) | 8,768 (67.6%) | **<0.00001** | 128 (20.9%) | 397 (21.6%) | 0.7 |
| Vasopressors | 4 (0.7%) | 1,064 (8.2%) | **<0.00001** | 4 (0.7%) | 12 (0.7%) | 1 |
| Comorbidities | | | | | | |
| Diabetes | 119 (19.4%) | 3,413 (26.3%) | **0.0002** | 119 (19.4%) | 336 (18.3%) | 0.6 |
| Heart Failure | 28 (4.6%) | 1,698 (13.1%) | **<0.00001** | 28 (4.6%) | 56 (3.1%) | 0.1 |
| Hypertension | 267 (43.6%) | 6,884 (53.0%) | **<0.00001** | 267 (43.6%) | 779 (42.4%) | 0.6 |
| LOS (median [IQR]) | 7 (4-10) | 8 (5-15) | **<0.00001** | 7 (4-10) | 6 (4-10) | **0.00004** |

**Figure 1: AKI rates in PTZ, SAM, and matched PTZ cohorts**

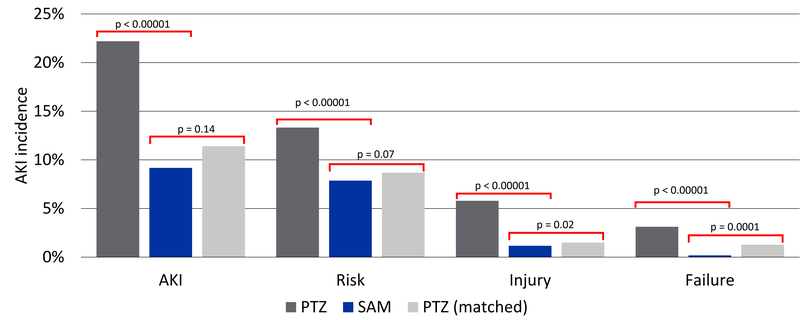


**Figure 2: AKI rates in matched cohort stratified by concomitant vancomycin therapy**

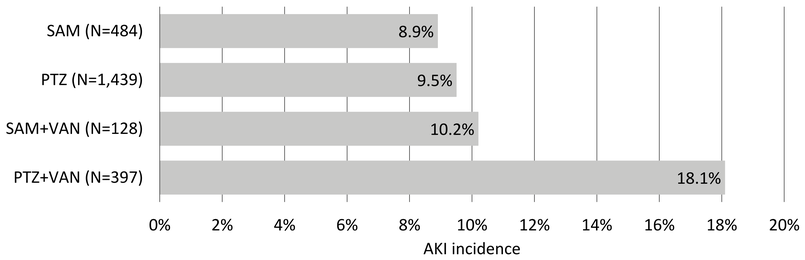


**Table 2: Multivariate regression results in matched cohort**

| Covariate | aOR | 95% CI | p |
|---|---|---|---|
| Treatment | | | |
| PTZ | (reference) | | |
| SAM | 0.87 | 0.60-1.24 | 0.5 |
| SAM + Vancomycin | 1.16 | 0.60-2.06 | 0.6 |
| PTZ + Vancomycin | 1.97 | 1.41-2.73 | 0.00005 |
| Charlson score (per point increase) | 1.03 | 1.00-1.06 | 0.04 |
| Length of stay (per day increase) | 1.03 | 1.02-1.04 | 0.00001 |

## Methods

- Clinical data was collected from the UK Center for Clinical and Translational Science from 9/1/2007 through 9/30/2015
- Adult patients were included if they received PTZ or SAM for ≥48 hours
- Patients were excluded for: pregnancy, cystic fibrosis, chronic kidney disease, baseline creatinine clearance (CrCl) < 30 mL/min
- Charlson Comorbidity index (CCI) was used to measure severity of illness
- CrCl was calculated with the adjusted Cockcroft-Gault equation
- Exposure to nephrotoxic drugs was defined as receiving at least 1 dose of the agent within 24 hours of PTZ or SAM initiation through discontinuation
- Hypotension was defined as MAP<65 mmHg, SBP<90 mmHg, or vasopressor exposure during PTZ or SAM treatment
- AKI was defined as meeting any of the RIFLE criteria
  - Risk: ≥ 25% decrease in CrCl
  - Injury: ≥ 50% decrease in CrCl
  - Failure: ≥ 75% decrease in CrCl
- Patients were matched on: hypotension, CCI, baseline CrCl, diabetes, hypertension, heart failure, and nephrotoxic drug exposures

## Conclusions

- AKI incidence was similar in patients treated with SAM and PTZ
- Adding VAN to PTZ significantly increased AKI incidence
- Administration of multiple beta-lactam agents is not the likely mechanism for increased AKI observed with PTZ and VAN

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