Published in final edited form as:

Pharmacotherapy. 2017 May ; 37(5): 593–598. doi:10.1002/phar.1918.

Acute kidney injury in patients treated with IV beta-lactam/beta-lactamase inhibitor combinations

W. Cliff Rutter^{1,2} and David S. Burgess¹

¹University of Kentucky College of Pharmacy, Lexington, KY

²University of Kentucky HealthCare, Lexington, KY

Abstract

Study Objective—Increased acute kidney injury (AKI) incidence has been reported in patients receiving piperacillin-tazobactam (PTZ) therapy compared to other beta-lactams. This study sought to determine if the addition of beta-lactamase inhibitors impact AKI incidence by comparing patients treated with PTZ or ampicillin-sulbactam (SAM).

Design—Retrospective cohort study

Setting—Large academic tertiary care hospital

Patients—Overall, 2,448 patients received PTZ (n=1,836) or SAM (n=612) for at least 48 hours between September 1, 2007 and September 30, 2015. Patients were excluded for pregnancy, cystic fibrosis, chronic kidney disease, and initial creatinine clearance (CrCl) < 30 mL/min. Patients were matched on Charlson Comorbidity Index (CCI), initial CrCl, hypotension exposure, various nephrotoxic drug exposures, history of diabetes, heart failure, and hypertension.

Measurements and Main results—AKI occurred in 265 patients at similar rates for both groups (PTZ 11.4% vs SAM 9.2%; p=0.14). After stratifying by vancomycin exposure and controlling for confounders, there was no difference in the risk of AKI for SAM or PTZ (adjusted OR 0.87, 95% CI 0.59–1.25). The addition of vancomycin to PTZ increased the likelihood of AKI compared to PTZ alone (adjusted OR 1.77, 95% CI 1.26–2.46). Concomitant SAM and VAN therapy was not associated with a significant increase in AKI compared to SAM monotherapy (adjusted OR 1.01, 95% CI 0.48–1.97).

Conclusion—Rates of AKI were similar for PTZ and SAM in a matched cohort. The addition of a beta-lactamase inhibitor is not likely the mechanism in the observed increased rates of AKI in patients treated with vancomycin and PTZ.

Keywords

Acute kidney injury; beta-lactam/beta-lactamase inhibitor combinations; vancomycin; piperacillin-tazobactam; ampicillin-sulbactam

Background

The use of piperacillin-tazobactam in combination with vancomycin has been associated with elevated rates of acute kidney injury (AKI) in many small retrospective studies. Incidence rates of AKI range from 9.5% to 34.8%, depending on the target population, with critically ill populations having higher incidence of AKI.^{1–8} The most common comparator agent in these studies was cefepime^{4–6}, because piperacillin-tazobactam and cefepime share a similar niche in antipseudomonal therapy. In these comparisons, piperacillin-tazobactam (PTZ) was associated with higher rates of AKI vs cefepime. The mechanism for the increased incidence of AKI is unknown. However, PTZ is unique, when compared to cefepime, in that it contains a beta-lactam as well as a beta-lactamase inhibitor that is structurally similar to other beta-lactams.

Ampicillin-sulbactam (SAM) is another intravenous beta-lactam/beta-lactamase inhibitor combination that is commonly used in practice. No studies examining the difference in AKI incidence between these 2 agents are available. The primary objective of this study was to determine if there is a significant difference in the rate of AKI in patients treated with PTZ or SAM. We hypothesize that these groups have similar rates of AKI and therefore the observed increase in AKI with PTZ is not related to co-administration of a beta-lactam with a beta-lactamase inhibitor.

Methods

This was an institutional review board-approved retrospective cohort study conducted at the University of Kentucky HealthCare between September 1, 2007 and September 30, 2015. Adult patients receiving PTZ or SAM for a least 48 hours were included. Exclusion criteria were current treatment with other beta-lactam agents, pregnancy, cystic fibrosis or chronic kidney disease, and an initial creatinine clearance (CrCl) less than 30 mL/min. To account for the effect of vancomycin on AKI, patients were stratified by vancomycin exposure.

The primary outcome was incidence of AKI as defined by the Risk Injury Failure Loss and End-stage (RIFLE) criteria, an established method of identifying AKI.⁹ Creatinine clearance was used as a marker for glomerular filtration rate (GFR) and was estimated by the adjusted Cockcroft-Gault equation.¹⁰ Exposure to other nephrotoxic agents was defined as receipt of at least one dose within the 24 hours prior to treatment initiation through treatment discontinuation. Nephrotoxic agents included in this analysis were aminoglycosides, amphotericin B, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, intravenous radiocontrast dye, loop diuretics, non-steroidal antiinflammatory drugs, calcineurin inhibitors, vancomycin, and vasopressors. Hypotension was defined as a composite of mean arterial pressure less than 65 mmHg, systolic blood pressure less than 90 mmHg, or vasopressor exposure during treatment. The Charlson comorbidity index (CCI) was used to approximate underlying severity of chronic illness.¹¹

Data collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT) included demographic data, drug dosing and administration data, laboratory data, and comorbidity data. The EDT contains electronic

medical record data from University of Kentucky HealthCare from 2006 to present. Data stored in the EDT includes patient demographics, financial classification (Medicare, Medicaid, private insurance), provider-level details, diagnoses, procedures, lab tests and results, medication administration, visit details (age, length of stay, etc.), and vital signs. Patients were followed from admission to discharge.

Results are reported using descriptive statistics. The Student's *t* test or the Wilcoxon's rank-sum test were used to compare continuous variables. Categorical variables were compared with chi-squared or Fisher's exact tests as appropriate. Patients in the PTZ and SAM groups were propensity score matched¹⁴ in a 3 to 1 fashion between PTZ and SAM groups based on CCI, initial CrCl (30–59, 60–89, and >90 mL/min), hypotension exposure, exposure to aminoglycosides, amphotericin B, ACE inhibitors, loop diuretics, calcineurin inhibitors, or vancomycin, history of diabetes, heart failure, or hypertension. These variables were selected based on unadjusted associations with AKI in bivariate analysis and were equally weighted in the final propensity score model. Variables were analyzed in bivariate logistic regression with AKI as the response variable. All variables that were significant in simple regressions were included in the initial multivariate logistic regression of AKI. Variables were removed from the multivariate model in a step-wise fashion to minimize the Akaike Information Criterion to maximize model fit for the final multivariate model. Goodness-of-fit was tested with the Hosmer-Lemeshow test and the area under the receiver-operator-characteristic curve (ROC) or *c*-statistic. All tests were two-tailed, with an alpha of 0.05 considered significant. All data analyses were performed using R v3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio v0.98 (RStudio, Inc., Boston, MA).^{12,13}

Results

Following matching, 2,448 patients were analyzed for the primary outcome, with 1,836 patients receiving PTZ and 612 receiving SAM. Baseline covariates were evenly distributed between groups (Table 1), with the exceptions of CCI (5 [IQR 2–9] vs. 4 [IQR 1–9] in SAM and PTZ groups, respectively; *p*=0.002) and IV radiocontrast dye exposure (3.3% vs. 5.8% in SAM and PTZ groups, respectively; *p*=0.02). Overall AKI incidence was similar between SAM (9.2%) and PTZ (11.4%, *p*=0.15). However, PTZ was associated with higher rates of GFR reductions compared with SAM (>50%: 1.5% vs. 1.1%, *p*=0.02; and >75%: 1.3% vs. 0.2%, *p*=0.0001) (Table 2).

Vancomycin exposure was significantly associated with AKI independent of treatment group on bivariate logistic regression (OR 1.07; 95% CI 1.04–1.1) (Table 3). The incidence of AKI was lowest in the SAM monotherapy group (8.9%) and highest in the PTZ plus vancomycin group (18.1%). The rates of AKI for PTZ monotherapy (9.5%) and SAM plus vancomycin (10.2%) were somewhat higher than SAM monotherapy. Following multivariate regression (Table 4), there were no difference in the odds of AKI between SAM and PTZ (aOR 0.87, 95% CI 0.59–1.25), however, the addition of vancomycin to PTZ significantly increased the odds of AKI compared to PTZ monotherapy (aOR 1.77, 95% CI 1.26–2.46). The addition of VAN to SAM therapy did not increase the odds of AKI (aOR 1.01; 95% CI 0.48–1.97).

Additional factors that independently predicted AKI were duration of beta-lactam therapy, history of heart failure, loop diuretic exposure, and calcineurin inhibitor exposure (Table 4). There was no evidence of overfitting in the model with a Hosmer-Lemeshow p value of 0.37, and the model had an AUC under the ROC of 0.71.

Discussion

In this large retrospective cohort study, the incidence of AKI between two common beta-lactam/beta-lactamase inhibitor combinations was similar after controlling for confounding factors associated with AKI. To our knowledge, this is the first study to examine this relationship.

The literature in this area describes a high variability in the rates of AKI associated with PTZ, mainly as combination therapy with vancomycin. Kim and colleagues reported the rate of PTZ monotherapy-associated AKI to be 15.4%, which was not significantly different from the combination therapy arm (18.8%).⁸ AKI rates when PTZ is combined with VAN range from 9.5 to 34.8%.^{1–8} Few studies have compared AKI incidence among different treatment regimens, but the most common comparator is cefepime. Gomes and colleagues found PTZ combined with VAN had significantly higher rates of AKI compared to the combination of cefepime and VAN (34.8% vs 12.5%).⁴ In a study of patients with diabetic osteomyelitis, PTZ-VAN was associated with a non-statistically significant higher rate of AKI (29.3%) compared with cefepime-VAN (13.3%).⁶ Additionally, in critically ill patients, no difference in AKI incidence was noted between PTZ or CFP when combined with VAN.⁵ These studies used varying definitions of AKI and examined relatively small sample sizes. Additionally, although cefepime and PTZ are commonly interchanged clinically, PTZ is distinct because of the addition of a beta-lactamase inhibitor to the beta-lactam. The unadjusted AKI rate in our study for patients in the PTZ arm was 22.2%; however, following matching the AKI rate was only 11.4% in the PTZ group (p=0.15). After stratification by vancomycin use, PTZ-VAN had higher rates of AKI compared to PTZ alone (18.1% vs. 9.5%; aOR 1.77; 95% CI 1.26–2.46), which is consistent with prior literature.

Ampicillin-sulbactam is another beta-lactam/beta-lactamase inhibitor combination used intravenously for the treatment of a variety of infections. Nephrotoxicity data for SAM are limited; however, one small study of high-dose SAM for multidrug resistant *Acinetobacter baumannii* pneumonia found AKI rates of approximately 15.3%.¹⁵ Another study, examining SAM use in multidrug resistant *A. baumannii* infections found AKI renal failure occurred in 26% of patients.¹⁶ These findings are limited by sample size and selection of critically ill patients, who have higher rates of nephrotoxicity. In contrast, we found that AKI occurred in 9.2% of patients receiving SAM. Distinct data for patients receiving SAM in combination with vancomycin is not readily available from earlier SAM studies. When stratified by vancomycin exposure, we found a numerical, but statistically insignificant, increase in AKI (10.2% SAM-VAN vs 8.9% SAM alone; aOR 1.01, 95% CI 0.48–1.97).

Despite the marked interest in the increase in nephrotoxicity noted with combination PTZ and VAN therapy, there have been no hypothesized pathophysiological mechanisms for this finding. We considered the addition of tazobactam to piperacillin as a possible contributing

factor to the increase in AKI due to the administration of two beta-lactam-like agents. This is specifically important when comparing PTZ-VAN with other beta-lactam combinations that contain only a single beta-lactam agent, such as cefepime or meropenem. Nephrotoxicity data for beta-lactamase inhibitors administered alone are lacking. Ampicillin-sulbactam is the only beta-lactam/beta-lactamase inhibitor agent commonly used as an alternative to PTZ at our institution. Our findings demonstrate that rates of AKI are similar among beta-lactam/beta-lactamase inhibitor combinations at our institution, and that the combination of vancomycin and piperacillin-tazobactam is a major factor in AKI.

This study is not without limitations. While we employed a robust analysis via matching patients on several possible confounders, there is still the possibility of unmeasured confounders in our sample. However, we did control for many nephrotoxic exposures, such as hypotension and other nephrotoxic drug administration, which should explain the majority of confounding in this study. Additionally, we attempted to control for the temporal relation of nephrotoxic exposure to the treatment window of the study agents. For other nephrotoxic agents, dose-response relationships were not assessed and all exposures were defined as receipt of at least one dose within 24 hours prior to initiation of study agents. This may overestimate the impact of those exposures on AKI, which in turn would bias our results towards the null hypothesis. Between-group differences in chronic illness, as assessed by the CCI, could bias results suggesting that SAM is more nephrotoxic than PTZ. However, our results show the opposite. Critical illness is not well captured by the CCI, and there is a chance that there was a higher proportion of critically ill patients in the PTZ arm. To counter this, we matched on presence of hypotension during the treatment period and baseline severity of illness. Finally, it is unclear if the nephrotoxic potentials of the beta-lactam agents are similar. Due to the timeframe of this study, no patients received piperacillin monotherapy, which precludes any inference regarding the additional nephrotoxic potential of tazobactam. Further prospective studies of combination antimicrobial chemotherapy are warranted, as are animal and human studies of the mechanism for increased nephrotoxicity.

Conclusion

The rates of AKI for piperacillin-tazobactam and ampicillin-sulbactam were similar in our large matched cohort study. Additionally, concomitant vancomycin exposure was associated with significant increases in AKI incidence. The magnitude of increase was significantly different for piperacillin-tazobactam compared to ampicillin-sulbactam.

Acknowledgments

The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1TR000117 and UL1TR001998.

References

1. Burgess LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. *Pharmacother J Hum Pharmacol Drug Ther.* 2014 Jul; 34(7):670–6.
2. Karino S, Kaye KS, Navalkele B, Nishan B, Salim M, Solanki S, et al. Epidemiology of acute kidney injury among patients receiving concomitant vancomycin and piperacillin-tazobactam:

- opportunities for antimicrobial stewardship. *Antimicrob Agents Chemother*. 2016 Jun; 60(6):3743–50. [PubMed: 27067325]
3. McCormick H, Tomaka N, Baggett S, Heierman T, LaFosse J, Gilbert S, et al. Comparison of acute renal injury associated with intermittent and extended infusion piperacillin/tazobactam. *Am J Health Syst Pharm*. 2015 Jun 1; 72(11_Supplement_1):S25–30. [PubMed: 25991590]
 4. Gomes DM, Smotherman C, Birch A, Dupree L, Della Vecchia BJ, Kraemer DF, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. *Pharmacother J Hum Pharmacol Drug Ther*. 2014 Jul; 34(7):662–9.
 5. Hammond DA, Smith MN, Painter JT, Meena NK, Lusardi K. Comparative incidence of acute kidney injury in critically ill patients receiving vancomycin with concomitant piperacillin-tazobactam or cefepime: a retrospective cohort study. *Pharmacother J Hum Pharmacol Drug Ther*. 2016 May; 36(5):463–71.
 6. Moenster RP, Linneman TW, Finnegan PM, Hand S, Thomas Z, McDonald JR. Acute renal failure associated with vancomycin and β -lactams for the treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. *Clin Microbiol Infect*. 2014 Jun; 20(6):O384–9. [PubMed: 24118354]
 7. Davies, SW., Efird, JT., Guidry, CA., Dietch, ZC., Willis, RN., Shah, PM., et al. Top guns: the “Maverick” and “Goose” of empiric therapy. *Surg Infect* [Internet]. 2015 Oct 20. [cited 2015 Dec 14]; Available from: <http://online.liebertpub.com/doi/10.1089/sur.2015.104>
 8. Kim, T., Kandiah, S., Patel, M., Rab, S., Wong, J., Xue, W., et al. Risk factors for kidney injury during vancomycin and piperacillin/tazobactam administration, including increased odds of injury with combination therapy. *BMC Res Notes* [Internet]. 2015 Dec. [cited 2015 Dec 14];8(1). Available from: <http://www.biomedcentral.com/1756-0500/8/579>
 9. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care Lond Engl*. 2004 Aug; 8(4):R204–212.
 10. Wilhelm SM, Kale-Pradhan PB. Estimating creatinine clearance: a meta-analysis. *Pharmacotherapy*. 2011 Jul; 31(7):658–64. [PubMed: 21923452]
 11. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011 Mar 15; 173(6):676–82. [PubMed: 21330339]
 12. R: A language and environment for statistical computing [Internet]. R Foundation for Statistical Computing; 2014. Available from: <http://www.R-project.org>
 13. RStudio Team. RStudio: Integrated Development for R [Internet]. Boston, MA: 2015. Available from: <http://www.rstudio.com/>
 14. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Polit Anal*. 2006 Dec 6; 15(3):199–236.
 15. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect*. 2008 Jun; 56(6):432–6. [PubMed: 18501431]
 16. Oliveira MS, Prado GVB, Costa SF, Grinbaum RS, Levin AS. Ampicillin/sulbactam compared with polymyxins for the treatment of infections caused by carbapenem-resistant *Acinetobacter* spp. *J Antimicrob Chemother*. 2008 Mar 13; 61(6):1369–75. [PubMed: 18367459]

Table 1

Patient demographics among matched cohort

Variable	SAM (N=612)	PTZ (N=1,836)	p
Age (median [IQR])	52 (42–62)	53 (40–63)	0.7
Male Gender	338 (55.2%)	954 (52.0%)	0.2
Caucasian Race	554 (90.5%)	1,648 (89.8%)	0.6
Weight, kg (mean[SD])	79.9 (22.4)	80.5 (23.8)	0.8
BMI (mean[SD])	27.7 (7.0)	27.8 (8.8)	0.9
CCI (median [IQR])	5 (2–9)	4 (1–9)	0.002
Initial CrCl (median [IQR])	100 (77.8–127.5)	103.9 (76.8–130.9)	0.4
Initial CrCl (mL/min)			0.8
30–59	64 (10.5%)	181 (9.9%)	
60–89	165 (27.0%)	482 (26.3%)	
90	383 (62.6%)	1,173 (63.9%)	
Hypotension	42 (6.9%)	144 (7.8%)	0.5
Comorbidities			
Diabetes	119 (19.4%)	336 (18.3%)	0.6
Heart Failure	28 (4.6%)	56 (3.1%)	0.1
Hypertension	267 (43.6%)	779 (42.4%)	0.6
Concomitant nephrotoxic agents			
Aminoglycoside	17 (2.8%)	36 (2.0%)	0.3
Amphotericin B	1 (0.2%)	3 (0.2%)	1
ACE inhibitor	88 (14.4%)	217 (11.8%)	0.1
ARB	25 (4.1%)	59 (3.2%)	0.4
IV Contrast	20 (3.3%)	107 (5.8%)	0.02
Loop diuretic	92 (15.0%)	242 (13.2%)	0.3
NSAID	106 (17.2%)	294 (16.0%)	0.5
Calcineurin inhibitors	21 (3.4%)	57 (3.1%)	0.8
Vancomycin	128 (20.9%)	397 (21.6%)	0.7
Vasopressors	4 (0.7%)	12 (0.7%)	1
Beta-lactam duration of therapy (days; median [IQR])	4 (2–5)	4 (3–6)	<0.00001
Vancomycin duration of therapy (days; median [IQR])	(N=128) 7 (4–11)	(N=397) 7 (4–13)	0.6

Data are N(%) unless specified otherwise. ACE – angiotensin converting enzyme; ARB – Angiotensin II receptor blocker; IQR – interquartile range; NSAID – nonsteroidal anti-inflammatory drug; PTZ – piperacillin-tazobactam; SAM – Ampicillin-sulbactam; SD – standard deviation

Table 2

Primary outcome

Outcome	SAM	PTZ	p-value
AKI	56 (9.15%)	209 (11.38%)	0.14
Risk	48 (7.84%)	159 (8.66%)	
Injury	7 (1.14%)	27 (1.47%)	
Failure	1 (0.16%)	23 (1.25%)	

AKI – acute kidney injury; PTZ – piperacillin-tazobactam; SAM – ampicillin-sulbactam; Risk: 25% decrease in CrCl; Injury: 50% decrease in CrCl; Failure: 75% decrease in CrCl

Table 3

Differences in AKI stratified by vancomycin exposure for patients treated with piperacillin-tazobactam or ampicillin-sulbactam

Outcome	SAM monotherapy (N=484)	PTZ monotherapy (N=1,439)	p-value	SAM+VAN (N=128)	PTZ+VAN (N=397)	p-value
AKI	43 (8.9%)	137 (9.5%)	0.74	13 (10.2%)	72 (18.1%)	0.038
Risk	38 (7.8%)	112 (7.8%)		10 (7.8%)	47 (11.8%)	
Injury	4 (0.8%)	15 (1.0%)		3 (2.3%)	12 (3.0%)	
Failure	1 (0.2%)	10 (0.7%)		0 (0%)	13 (3.3%)	

AKI – acute kidney injury; PTZ – piperacillin-tazobactam; SAM – ampicillin-sulbactam; VAN – vancomycin; Risk: 25% decrease in CrCl; Injury: 50% decrease in CrCl; Failure: 75% decrease in CrCl

Table 4

Bivariate and Multivariate AKI associations

Variable	Bivariate			Multivariate		
	OR	95% CI	p	aOR	95% CI	p
<i>Treatment characteristics</i>						
Treatment group						
PTZ		(reference)			(reference)	
SAM	0.93	0.64 – 1.32	0.678	0.87	0.59 – 1.25	0.465
SAM+VAN	1.07	0.56 – 1.89	0.815	0.88	0.44 – 1.61	0.691
PTZ+VAN	2.11	1.54 – 2.86	<0.001	1.77	1.26 – 2.46	0.001
Duration of beta-lactam therapy (per day increase)	1.12	1.08 – 1.16	<0.001	1.08	1.04 – 1.12	<0.001
<i>Patient characteristics</i>						
Age (per year increase)	1	0.99 – 1.01	0.875			
CCI (per point increase)	1.01	0.98 – 1.04	0.348			
Male gender	1.19	0.92 – 1.54	0.187			
Caucasian race	1.14	0.75 – 1.81	0.57			
<i>Baseline creatinine clearance (mL/min)</i>						
30–59		(reference)			(reference)	
60–59	0.59	0.36 – 0.98	0.039	0.64	0.38 – 1.10	0.1
90	1.15	0.76 – 1.80	0.521	1.55	1.00 – 2.50	0.062
Heart failure	2.52	1.45 – 4.18	0.001	2.06	1.11 – 3.66	0.016
Diabetes	1.39	1.02 – 1.88	0.034	1.32	0.94 – 1.83	0.104
Hypertension	1.12	0.87 – 1.45	0.374			
Hypotension [†]	2.05	1.37 – 3.00	<0.001			
<i>Concomitant nephrotoxins</i>						
Aminoglycoside	2.76	1.40 – 5.10	0.002	1.89	0.88 – 3.78	0.086
Amphotericin B	2.75	0.14 – 21.59	0.381			
ACE inhibitor	1.24	0.85 – 1.77	0.239			
ARB	0.51	0.18 – 1.15	0.151			

Variable	Bivariate			Multivariate		
	OR	95% CI	p	aOR	95% CI	p
IV Radiocontrast Dye	0.94	0.50 – 1.63	0.826			
Loop diuretic	3.59	2.68 – 4.79	<0.001	3.06	2.22 – 4.19	<0.001
Calcineurin inhibitor	3.44	2.02 – 5.65	<0.001	4.28	2.42 – 7.35	<0.001
NSAID	0.79	0.54 – 1.12	0.2			
Vasopressor	2.77	0.77 – 8.02	0.079			

AKI – acute kidney injury; ACE – angiotensin converting enzyme; aOR – adjusted odds ratio; ARB – angiotensin II receptor antagonist; CCI – Charlson Comorbidity Index; CI – confidence interval; NSAID – nonsteroidal anti-inflammatory drug; OR – odds ratio; PTZ – piperacillin-tazobactam; SAM – ampicillin-sulbactam; VAN – vancomycin;

[‡]Hypotension removed during AIC minimization step of multivariate analysis