Frequency of and Risk Factors for Acute Kidney Injury Associated With Vancomycin Use in the Pediatric Intensive Care Unit

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BACKGROUND: Published information evaluating frequency of and risk factors for vancomycin-induced acute kidney injury (AKI) in the pediatric intensive care unit (PICU) population is conflicting.

OBJECTIVES: The primary objective was to describe the proportion of our PICU patients who developed AKI with intravenous (IV) vancomycin. The secondary objective was to describe the associated potential risk factors.

METHODS: Pediatric patients (0-18 years) who received their first IV vancomycin dose in the PICU were evaluated in this retrospective chart review. AKI was defined based on Pediatric-Modified RIFLE (pRIFLE) criteria. Patient demographics, vancomycin trough concentrations, concomitant nephrotoxins, and estimated creatinine clearance changes were analyzed.

RESULTS: Of 265 patients included, the primary outcome of AKI (defined by meeting any pRIFLE criteria) occurred in 62 (23.4%) patients (48 category R, 11 category I, 3 category F). Patients who received vancomycin treatment for ≥ 5 days were more likely to develop AKI (unadjusted odds ratio [uOR]: 2.52; 95% confidence interval [CI]: 1.11-5.73), as were patients with a maximum vancomycin trough level ≥ 20 mg/L (OR: 2.99; 95% CI: 1.54-5.78) and patients on 1 (uOR: 2.29; 95% CI: 1.12-4.66) or more concurrent nephrotoxin (uOR: 3.11; 95% CI: 1.43-6.77). Among nephrotoxins, patients receiving furosemide concomitantly with vancomycin were more likely to develop AKI (uOR: 3.47; 95% CI: 1.92-6.27). After adjustment, only furosemide was a significant predictor of risk of AKI/AKI (adjusted OR: 3.52; 95% CI: 1.88-6.62). The study was limited by its retrospective and observational design, and confounding variables.

CONCLUSIONS: Patients who were receiving vancomycin with concurrent furosemide were at highest risk of developing AKI.

INDEX TERMS: acute kidney injury, critical illness, drug monitoring, pediatrics, vancomycin

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INTRODUCTION

Vancomycin is an antibiotic often used as first-line therapy for the treatment of serious Gram-positive infections, especially methicillin-resistant *Staphylococcus aureus* (MRSA).¹ Recent guidelines recommend serum trough concentrations be maintained above 10 mg/L to avoid resistance, and to target 15 to 20 mg/L in complicated infections (e.g., bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S aureus*).¹ The 2011 Infectious Disease Society of America MRSA treatment guidelines acknowledged the lack of pediatric efficacy and safety evidence for targeting trough

concentrations of 15 to 20 mg/L, but current guidelines still recommend that it be considered for serious infections.²

Regardless of etiology, up to 82% of patients admitted to a pediatric intensive care unit (PICU) develop acute kidney injury (AKI) defined by any pediatric modified RIFLE criteria (pRIFLE; i.e., Risk, Injury, Failure, Loss, End-stage renal disease), and AKI is an independent risk factor for death.³ pRIFLE criteria is a method to define the risk of RIFLE in the pediatric population from the change in estimated creatinine clearance (eCCL) (Table 1).

Vancomycin use has been associated with nephrotoxicity (drug-induced AKI) for decades.

Table 1. Acute Kidney Injury Defined As pRIFLE Category

Category	Definition
R	eCCL decrease by 25%-49%
I	eCCL decrease by > 50%-74%
F	eCCL decrease by > 75%

eCCL, estimated creatinine clearance; pRIFLE, pediatric-modified RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease)

The exact mechanism of vancomycin-induced renal damage is still unknown, but it is postulated that proximal renal tubular cell necrosis occurs by vancomycin accumulation causing oxidative stress.¹ Vancomycin is almost exclusively eliminated renally, mainly via glomerular filtration and some active tubular secretion, so renal dysfunction also impacts vancomycin levels.¹ Estimates of the incidence of AKI associated with vancomycin in pediatrics range from 5% to 27.2%.^{4,9} However, evidence is conflicting regarding the relationship between PICU admission, vancomycin use, and AKI. McKamy et al⁴ studied children on vancomycin in all hospital wards (n = 167) and defined AKI as a 50% baseline increase in serum creatinine (SCr) or an increase of 0.5 mg/dL. AKI occurred in 24 of 167 patients (17%). The PICU patients had a significantly higher (p < 0.001) frequency of AKI than those without a PICU stay; and trough concentrations of ≥ 15 mg/L in pediatric patients were associated with a threefold increased risk of developing AKI. Knoderer et al⁵ studied children on vancomycin in all hospital wards (n = 859) and AKI was defined as meeting pRIFLE category I (Table 1). They found that 167/859 patients experienced AKI. Among these patients, 96 were admitted to PICU (odds ratio [OR]: 1.86; 95% confidence interval [CI]: 1.20-2.94) and 21 had initial vancomycin trough concentrations >15 mg/L (OR: 2.18; 95% CI: 1.21-3.92).⁵ Of note, studies have shown that there is no association between AKI and total daily dose of vancomycin, rather that the serum levels of vancomycin are the important factor in development of AKI.^{4,5,7}

Totapally et al⁷ performed a retrospective analysis on PICU patients who received vancomycin for at least 3 days (n = 391 courses) with AKI defined as pRIFLE category I (Table 1). AKI occurred in 49 (17%) of 284 patient vancomycin courses. Administration of nephrotoxic drugs before vancomycin therapy was associated with AKI (OR: 2.23; 95% CI: 1.27-3.93). There was

no significant difference in trough vancomycin concentrations between the 2 groups. Cies et al⁸ demonstrated that maintaining vancomycin trough concentrations > 15 mg/L was not associated with an increased rate of renal injury when compared with beta-lactam monotherapy in the PICU population. Most recently, Sinclair et al⁹ reported that concurrent use of nephrotoxic medications, and longer duration of therapy were associated with increased odds of AKI (defined as pRIFLE category I; Table 1). Also, maximum trough concentrations in the initial 96 hours of therapy were higher in patients with AKI (p = 0.021).

The frequency of AKI in PICU patients on vancomycin thus ranges from 7% to 22% and an association with trough levels is not consistent.^{4,6-9} A study of risk factors specifically in PICU patients is necessary to improve the understanding of AKI risk with vancomycin, including analysis of vancomycin factors (duration, trough levels) and other independent risk factors, such as concomitant nephrotoxins.

The primary objective of our study was to describe the proportion of PICU patients who developed AKI while receiving intravenous (IV) vancomycin. AKI is defined throughout this paper as meeting any pRIFLE criteria (Table 1) unless otherwise specified. The secondary objective was to evaluate which risk factors (age, concomitant medications, vancomycin trough levels, and duration of therapy) were associated with AKI in PICU patients on vancomycin.

MATERIALS AND METHODS

Study Population

The study was approved by the local University Conjoint Health Research Ethics Board and the need for informed consent was waived. Patients admitted to the PICU and prescribed IV vancomycin between May 2011 and March 2014 were evaluated for inclusion in this retrospective chart review. Pediatric patients (<18-years-old) who received their first dose of a course of IV vancomycin therapy (minimum of 3 doses) in the PICU, had 1 or more vancomycin trough concentrations (drawn within 60 minutes of the scheduled third or later dose), had a baseline SCr value (prior to or within 4 hours of vancomycin initiation), as well as at least 1 SCr measured more than 4 hours after initiation of vancomycin.

cin were included in the study. Patients who received dialysis (intermittent hemodialysis, peritoneal dialysis, or continuous renal replacement therapy) prior to vancomycin administration were excluded. For patients with multiple vancomycin courses/admissions, only the initial vancomycin course from the first admission was included. However, if a patient did not meet the inclusion criteria with the initial vancomycin course, subsequent courses were eligible for inclusion provided inclusion criteria were met (to a maximum of 1 course included per patient).

Data Collection

Data were collected from the electronic charting system in place at our center. Data collected included: age, sex, weight, height, SCr values (baseline, maximum, and last value prior to discharge home), vancomycin trough concentrations and relation to vancomycin doses (initial, steady state, maximum concentration), and duration of vancomycin therapy (days). Concomitant nephrotoxic medication use was evaluated for the following agents: angiotensin-converting-enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARBs), inotropes, vasopressors, scheduled non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, furosemide, calcineurin inhibitors (i.e., cyclosporine or tacrolimus), and acyclovir. Date and time of all relevant trough levels and SCr levels were recorded. Trough concentrations were examined rather than total daily doses of vancomycin as studies have shown that there is no association between AKI and total daily doses.^{4,5,7}

Outcomes

The primary outcome of the study was the proportion of patients who developed AKI as defined by any pRIFLE category (Table 1). The highest SCr value throughout the first course of vancomycin therapy was used to determine the eCCL endpoint. The Schwartz equation, $eCCL = k (\text{height}) / \text{SCr}$, was used to calculate the eCCL ($\text{mL}/\text{min}/1.73 \text{ m}^2$).¹⁰ The value of k was 0.45 for infants up to 1 year of age, 0.55 for children (1-13 years of age), and adolescent girls (13-18 years of age), and 0.7 for adolescent boys (13-18 years of age).¹⁰ When a patient's height was not recorded in the chart, the 50th percentile of height for weight value from the World Health Organization growth charts adapted for Canada

was used as an estimated height.¹¹

The secondary outcome was to evaluate whether development of AKI was associated with patient age, vancomycin troughs, baseline renal dysfunction (defined as an eCCL < 67% of the mean values from Schwartz 2007),¹⁰ the use of any or a combination of nephrotoxic agents during vancomycin therapy, or length of vancomycin treatment.

Statistical Analysis

The study population was described using median and interquartile range for non-normally distributed data, and proportions for categorical data. The population was stratified based on those who developed AKI and those who did not. Medians were compared using Mann-Whitney U tests, while categories were compared using the χ^2 test (cells ≥ 5 individuals) or the Fisher's exact test (cells < 5 individuals). Secondary outcomes of association between factors and the development of AKI are reported as unadjusted ORs (uORs) with 95% CIs, calculated using univariate logistic regression. Adjusted ORs (aORs) and 95% CIs were produced using the forward selection procedure while including clinically relevant variables (age, sex, baseline renal dysfunction, treatment duration, initial trough concentration, maximum trough concentration, number of nephrotoxins, receipt of vasopressor/inotropes, receipt of acyclovir, and receipt of concurrent furosemide) in the logistic regression model.

Using a finite population correction, a 95% level of confidence, and an identified proportion of 23.4% for development of risk of AKI/AKI in our sample, our sample size of 265 provides a standard error of 0.026 and a precision of 5% for our primary outcome.

RESULTS

A total of 483 courses of vancomycin were screened from the database. Among the 218 courses excluded, 62 (28.4%) were less than 3 doses, 24 (11.0%) did not have an initial SCr value, 52 (23.8%) did not have a SCr value measured while on vancomycin, 8 (3.7%) received dialysis prior to their first vancomycin dose, and 39 (17.9%) did not have a vancomycin trough level measured. In addition, a total of 33 courses (15.1%) were excluded as repeated courses (10 patients).

After exclusion criteria were applied, a total

of 265 patients were included (1 course of vancomycin per patient). The primary outcome of AKI occurred in 62 (23.4%; 95% CI: 18.4%-28.4%) patients. Of the 62 patients, 48 (18% of the total) met pRIFLE criteria R, 11 (4.2% of the total) met criteria I, and 3 (1.1% of the total) met criteria F. Patient characteristics by primary outcome are shown in Table 2. Ninety-five percent of patients did not have a height recorded in the chart and so estimated heights were used. Overall, 6% patients had renal dysfunction prior to initiation of vancomycin, and eCCL change was calculated based on the already elevated SCr in these patients. Of the 62 patients who developed AKI (any category; Table 1), 45 (72.3%) returned to baseline renal function upon discharge. Eight of the 62 patients did not have a repeat SCr drawn after their maximum SCr, and 9 patients were still on vancomycin when their repeat SCr was measured before discharge from hospital. The time to maximum SCr for the AKI group was less than 2 days in 50% of the patients.

Secondary outcomes of associations are shown in Table 3. Logistic regression revealed that sex, age, and baseline renal dysfunction were not associated with AKI development, although there were a low number of patients with baseline renal dysfunction. Covariates that showed a significant unadjusted association with AKI included vancomycin treatment for ≥ 5 days (uOR: 2.52; 95% CI: 1.11-5.73) relative to treatment for <5 days, maximum vancomycin trough level ≥ 20 mg/L (uOR: 2.99; 95% CI: 1.54-5.78) relative to a maximum trough concentration of < 10 mg/L, and use of 1 (uOR: 2.29; 95% CI: 1.12-4.66) or > 1 concurrent nephrotoxin (uOR: 3.11; 95% CI: 1.43-6.77) relative to no nephrotoxin use. Of note, maximum vancomycin trough concentration ≥ 15 mg/L and < 20 mg/L did not show an increased AKI relative to a maximum trough value < 10 mg/L. Only inotropes, acyclovir, and furosemide could be analyzed as individual nephrotoxins because the proportions of patients receiving concurrent scheduled NSAIDs, ACEI/ARBs, and aminoglycosides were too small to be further analyzed. No patients were on calcineurin inhibitors (i.e., cyclosporine or tacrolimus). Patients receiving concomitant furosemide were more likely to develop risk of AKI/AKI (uOR: 3.47; 95% CI: 1.92-6.27) compared to those who did not receive furosemide concurrently with vancomycin; however, there was no association

seen with acyclovir and inotropes. After adjustment, only receipt of concurrent furosemide was found to be significantly associated with AKI (aOR: 3.52; 95% CI: 1.88-6.62).

DISCUSSION

The primary objective of this study was to determine the proportion of patients who developed AKI while receiving IV vancomycin therapy in the PICU. While we found that 23.4% of our study population developed AKI (any category), the frequency of pRIFLE category I and F (5.3%) was slightly lower than previously reported rates of pRIFLE category I in the PICU.^{7,9} Totapally et al⁷ and Sinclair et al⁹ found that 17.2% and 13.7% of patients developed pRIFLE category I, respectively, which is threefold greater than our result of 5.3% that developed either category I or F. This may be due to the fact that our study did not include repeat courses of vancomycin for individual patients.⁷

Our results on concomitant risk factors are overall similar to the results in the current literature. Duration of treatment of ≥ 5 days (uOR: 2.52; 95% CI: 1.11-5.73) and maximum trough concentration of ≥ 20 mg/L (uOR: 2.99; 95% CI: 1.54-5.78) were associated with AKI in the unadjusted statistical model. However, these factors were non-significant in the adjusted model. Similar to our unadjusted results, both Cies et al⁴ and McKamy et al⁶ found an association between a trough values of ≥ 20 mg/L and AKI. Conversely, Totapally et al⁷ did not find any association between trough concentrations and AKI. Interestingly, Sinclair et al⁹ did not include trough concentrations in their multiple logistic regression analysis, but maximum troughs were significantly higher in patients who developed AKI.

Concomitant use of furosemide was the only risk factor analyzed that was significant with both unadjusted and adjusted OR with AKI. Based on this, we conducted stratified analyses and found that individuals who received ≥ 5 days of vancomycin therapy and those who had a maximum trough concentration of ≥ 20 mg/L were more likely to receive furosemide during or immediately after their course of vancomycin, which explains the unadjusted results seen.

There is a complex interplay of AKI risk factors at work in the PICU, given that patients with

Table 2. Characteristics of Patients Treated With Vancomycin, by AKI Development (Any pRIFLE Category)

Demographics (Overall n = 265)	No AKI, n = 203 (76.6%)*	AKI, n = 62 (23.4%)*	p Value
Female	86 (42.4%)	24 (38.7%)	0.61
Age			0.143
<30 days	26 (12.8)	4 (6.4)	
30 days-<6 mo	25 (12.3)	13 (21.0)	
6 mo-<2 yr	48 (23.6)	20 (32.2)	
2-< 13 yr	81 (39.9)	21 (33.9)	
13-18 yr	23 (11.3)	4 (6.4)	
Median weight, kg (IQR)	12.40 (18.0)	10 (13.3)	0.26
Median height, cm (IQR)	90.00 (62.5)	78.5 (42.8)	0.40
Baseline renal dysfunction†	14 (6.9%)	2 (3.2%)	0.38
Duration of treatment (days)			0.04
<2	53 (26.1)	11 (17.7)	
2-5	107 (52.7)	28 (4.7)	
≥5	43 (21.2)	23 (37.1)	
Time to max SCr (days)‡			N/A
<2 (n = 62)		31 (50.0)	
2-5 (n = 61)		24 (39.3)	
≥5 (n = 24)		7 (29.2)	
Return to baseline renal function§		45 (72.3)	N/A
Initial trough (mg/L)			0.98
<10	116 (57.1)	37 (59.7)	
10-<15	57 (28.1)	17 (27.4)	
15-<20	19 (9.3)	5 (8.1)	
≥ 20-31.8	11 (5.4)	3 (4.8)	
Maximum trough (mg/L)			0.007
<10	44 (21.7)	9 (14.5)	
10-<15	69 (40.0)	15 (24.2)	
15-<20	49 (24.1)	12 (19.4)	
≥ 20-77	41 (20.2)	26 (41.9)	
Nephrotoxins			
ACEI/ARB	3 (1.5)	1 (1.6)	1.00
Inotropes	54 (26.6)	19 (30.6)	0.59
Furosemide	57 (28.1)	36 (58.1)	<0.001
Acyclovir	30 (14.8)	9 (14.5)	0.67
NSAIDs (scheduled)	12 (5.9)	3 (4.8)	1.00
Aminoglycosides	5 (2.5)	2 (3.2)	0.67
Nephrotoxins¶			0.01
0	87 (42.8)	14 (22.6)	
1	76 (37.4)	28 (45.2)	
≥2	40 (19.7)	20 (32.2)	

ACEI, angiotensin-converting-enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; pRIFLE, pediatric Risk, Injury, Failure, Loss, End-stage renal disease; SCr, serum creatinine

*Unless otherwise indicated

†Defined as eCLL < 67% of the mean value from Schwartz et al¹⁰

‡Only the patients who developed AKI have results for this category. Therefore, the n in each division of this category has been adjusted for duration of treatment

§Eight patients did not have a repeat SCr drawn after maximum SCr; therefore, they were not included in the resolved AKI group

¶ Number of nephrotoxins each patient was on while receiving vancomycin

Table 3. Unadjusted and Adjusted Estimates for Odds of AKI (Any pRIFLE Criteria) During Vancomycin Therapy

Covariate	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex		
Female	1.00 (ref)	Not included in final model
Male	0.77 (0.25-2.37)	
Age		Not included in final model
0-<30 days	0.88 (0.20-3.95)	
30 days-<6 mo	2.99 (0.85-10.49)	
6 mo-<2 yr	2.40 (0.73-7.82)	
2-<13 yr	1.49 (0.46-4.78)	
13-18 yr	1.00 (ref)	
Baseline renal dysfunction		
No	1.00 (ref)	Not included in final model
Yes	0.45 (0.10-2.04)	
Duration of treatment (days)		
< 2	1.00 (ref)	Not included in final modal
2-<5	1.27 (0.59-2.75)	
≥5	2.52 (1.11-5.73)	
Initial trough (mg/L)		Not included in final model
<10	1.00 (ref)	
10-14	0.94 (0.49-1.80)	
15-19	0.83 (0.29-2.36)	
≥20	0.86 (0.23-3.23)	
Maximum trough (mg/L)		
<10	1.00 (ref)	1.00 (ref)
10-14	1.06 (0.43-2.64)	0.82 (0.31-2.13)
15-19	1.20 (0.46-3.11)	0.87 (0.32-2.40)
≥20	3.10 (1.30-7.39)	2.48 (0.98-6.25)
Nephrotoxin		Not included in final model
0	1.0 (ref)	
1	2.29 (1.12-4.66)	
≥2	3.11 (1.43-6.77)	
Inotropes		Not included in final model
No	1.00 (ref)	
Yes	1.19 (0.67-2.21)	
Acyclovir		
No	1.00 (ref)	Not included in final model
Yes	0.84 (0.37-1.88)	
Furosemide		
No	1.00 (ref)	1.00 (ref)
Yes	3.47 (1.92-6.27)	3.52 (1.88-6.62)

AKI, acute kidney injury; CI, confidence interval; OR, odds ratio; pRIFLE, pediatric Risk, Injury, Failure, Loss, End-stage renal disease; ref, reference number for logistic regression

more severe illness have higher target vancomycin concentrations, may be on vancomycin longer, may require furosemide as part of their treatment more often, and are at higher risk of AKI. A patient only had to receive 1 dose of furosemide

during vancomycin therapy or within 24 hours of the last vancomycin dose to be included as a furosemide user. The indication for the use of furosemide in the patients studied was not known or recorded in data collection. Therefore, it is dif-

difficult to delineate whether furosemide was used to increase urine output after vancomycin caused AKI, or if furosemide was the cause of AKI itself. McKamy et al⁴ found that 71% of patients who experienced AKI were on furosemide (58% in our study). Cies et al⁶ (2013) stated 100% of patients in each group received a diuretic (furosemide or furosemide plus chlorothiazide) during their course of vancomycin, thus diuretic therapy was not included in the univariate analysis. Totapally et al,⁵ Knoderer et al,⁷ and Sinclair et al⁹ did not include furosemide as a nephrotoxin in their model. Cies et al⁸ collected concomitant diuretic use data, but separate analysis of diuretics from all nephrotoxins or vasoactive medications with the primary outcome was not included.

Unfortunately, the number of patients in our study using NSAIDs, aminoglycosides, and ACEI/ARBs was too small to have any meaningful results. Overall, in our study 77.4% of patients in the risk of AKI/AKI group were on ≥ 1 nephrotoxin.

Fifty percent of those who developed pRIFLE category I ($n = 14$) and 79.2% of those who developed AKI (any category) ($n = 48$) returned to baseline renal function before discharge. However, 8 patients did not have repeat SCr measurements before discharge. These 8 patients were categorized as not returning to baseline renal function, thus our result of 79.2% returning to baseline may be slightly elevated. Totapally et al⁷ had 87% of patients who developed AKI return to baseline.

One of the strengths of this study is that the pRIFLE eCCL criteria was chosen as a measure of AKI, instead of changes in SCr. Measuring eCCL changes is a more sensitive measure of AKI and more clinically relevant.³ Even though 95% of patient heights were estimated using growth charts, this was done consistently, and eCCL remains a better indicator of renal function.¹¹ We also included patients with pre-existing renal failure, increasing the generalizability of the results of our study.⁷

The limitations of the study include its observational and retrospective nature. Previous studies focused on pRIFLE category I; however, we combined all pRIFLE categories into our primary outcome, which limits our ability to compare results. This was done to increase our statistical power, as there were relatively few patients meeting pRIFLE category I. eCCL may

be a more sensitive measure of AKI; however, we had to estimate 95% of our patients' heights using the 50% percentile, which may have led to inaccuracies in eCCL calculations.

Our results may be confounded by severity of illness, as AKI is not uncommon in PICU patients.³ Indeed, identification of duration of vancomycin therapy, use of furosemide, and maximum trough level as risk factors for AKI support the theory that more severe illness is related to higher risk of AKI. After adjustment for all covariates, only furosemide was still significantly associated with risk of AKI. With regards to reasons for exclusion of patients, 52.7% were excluded for missing data (i.e., vancomycin trough concentrations, SCr levels). This may have biased our results as more lab work is often needed for more severely ill patients. Lastly, we relied on a handwritten list of patients who received dialysis, thus cannot be certain that every dialysis patient was eliminated.

In our study, 11% of vancomycin courses were excluded for not having a baseline SCr value, and 23.8% were excluded for not having a SCr value measured while on vancomycin therapy. These are both important components of monitoring for vancomycin toxicity, in order to detect a change in renal function. Another preventable pitfall in vancomycin monitoring is inappropriately drawn vancomycin trough levels. These occurred in 17.9% of courses in our study, but the reasons were not recorded. These factors can serve as reminders for all clinicians to remain diligent in ensuring proactive and correct monitoring throughout vancomycin therapy.

CONCLUSION

The primary outcome of AKI in patients receiving IV vancomycin occurred in 23.4% of PICU patients. After adjustment, only concomitant use of furosemide with vancomycin was associated with AKI. These results are similar to those in recently published studies with similar designs.^{7,9} Awareness of the factors associated with risk of AKI in these patients will help clinicians target these patients for diligent monitoring.

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Abbreviations ACEI, angiotensin-converting-enzyme inhibitor; AKI, acute kidney injury; aOR, adjusted odds ratio; ARB, angiotensin II receptor blocker; CI, confidence interval; eCCL, estimated creatinine clearance; IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NSAID, scheduled non-steroidal anti-inflammatory drug; OR, odds ratio; PICU, pediatric intensive care unit; pRIFLE, pediatric-modified RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease); SCr, serum creatinine; uOR, unadjusted odds ratio

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