Piperacillin/Tazobactam and Antibiotic-Associated Acute Kidney Injury in Critically Ill Children

Emily L. Joyce,[1,2,3] Sandra L. Kane-Gill,[2,4,5,6] Priyanka Priyanka,[2,3] Dana Y. Fuhrman,[1,2,3,6] and John A. Kellum[2,3,6]

[1]Division of Nephrology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [2]Department of Critical Care Medicine, Center for Critical Care Nephrology, [3]Department of Critical Care Medicine, CRISMA Center (Clinical Research, Investigation, and Systems Modeling of Acute Illness), and [6]Department of Critical Care Medicine, UPMC University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [4]Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania; and [5]Department of Pharmacy, UPMC, Pittsburgh, Pennsylvania

ABSTRACT

Background There continues to be uncertainty about whether piperacillin/tazobactam (TZP) increases the risk of AKI in critically ill pediatric patients. We sought to compare rates of AKI among critically ill children treated with TZP or cefepime, an alternative frequently used in intensive care units, with and without vancomycin.

Methods We conducted a retrospective cohort study assessing the risk of AKI in pediatric intensive care unit patients after exposure to vancomycin, TZP, and cefepime, alone or in combination, within 48 hours of admission. The primary outcome was development of stage 2 or 3 AKI or an increase in AKI stage from 2 to 3 within the 6 days after the 48-hour exposure window. Secondary outcomes included lengths of stay, need for RRT, and mortality.

Results Of 5686 patients included, 494 (8.7%) developed stage 2 or 3 AKI. The adjusted odds of developing AKI after medication exposure were 1.56 for TZP (95% confidence interval [95% CI], 1.23 to 1.99), 1.13 for cefepime (95% CI, 0.79 to 1.64), and 0.86 for vancomycin (95% CI, 0.69 to 1.07). The adjusted odds of developing AKI for vancomycin plus TZP versus vancomycin plus cefepime was 1.38 (95% CI, 0.85 to 2.24).

Conclusions Observational data in critically ill children show that TZP use is associated with increased odds of AKI. A weaker, nonsignificant association between vancomycin plus TZP and AKI compared with vancomycin plus cefepime, creates some uncertainty about the nature of the association between TZP and AKI. However, cefepime is an alternative not associated with AKI.

JASN 30: ●●●–●●●, 2019. doi: https://doi.org/10.1681/ASN.2018121223

AKI is prevalent and associated with serious consequences in critically ill children. The rate of severe AKI was measured at 11.6% of intensive care unit (ICU) admissions in a recent international study, with adjusted increased odds of death by 1.77 (95% confidence interval [95% CI], 1.17 to 2.68).[1] Furthermore, multiple studies have demonstrated association between AKI and prolonged mechanical ventilation, hospital and ICU length of stay, delay in recovery of other organ systems, and increased health care costs.[2–7] Aside from supportive care, the dearth of effective treatment has led to research focused on AKI prevention, including avoidance of nephrotoxins that cause

Received December 13, 2018. Accepted August 7, 2019.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Emily L. Joyce, Division of Nephrology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, 3347 Forbes Avenue, Suite 220, Pittsburgh, PA 15213. Email: emilylaurenjoyce@gmail.com

or contribute to AKI. Medication-associated AKI is common in critically ill children, with the odds of developing AKI increasing by 2.3 after administration of a β-lactam antibiotic in one study.[6] The combination of vancomycin (glycopeptide antibiotic) and piperacillin/tazobactam (β-lactam antibiotic) is often given to provide broad antibiotic coverage in children with a suspected bacterial infection until a pathogen can be identified and coverage narrowed. Recent evidence suggests an increased risk of AKI when these medications are given concomitantly,[8–14] but the pediatric critically ill population remains understudied. Furthermore, available evidence has been limited by small sample size and inadequate control for indication bias. It is prudent to understand the risk of AKI when vancomycin and piperacillin/tazobactam (TZP) are coadministered in these children and assess possible alternative agents to TZP while still providing antipseudomonal coverage. Cefepime, another β-lactam antibiotic, may serve this purpose in the appropriate clinical setting. Thus, we sought to compare rates of AKI among critically ill children treated with TZP or cefepime, with and without vancomycin, while controlling for various susceptibilities, severity of illness, and other common exposures in the ICU. We also used a propensity score to analyze the effect of indication bias.

Significance Statement

Antibiotic-associated AKI is prevalent and contributes to substantial morbidity and mortality in critically ill pediatric patients. Little is known about how empiric use of broad-spectrum antibiotics affects development of AKI. The authors show that treatment of critically ill children with piperacillin/tazobactam within the first 48 hours of intensive care unit admission is associated with subsequent development of AKI. They demonstrate a weaker, nonsignificant association between AKI and piperacillin/tazobactam used in combination with vancomycin in this population. This second finding adds to uncertainty about the nephrotoxicity of piperacillin/tazobactam in this highly susceptible population. Cefepime, a potential alternative antibiotic, which was not associated with AKI in the study, may be a suitable alternative for some indications.

METHODS

Study Design and Patient Population

We conducted a retrospective, inception cohort study, assessing the risk of AKI in pediatric critically ill patients after exposure to vancomycin, TZP, and cefepime, alone and in combination. We used the Peds HiDenIC (pediatric high-density intensive care) database, which includes patients aged ≥60 days admitted to the pediatric or cardiac ICUs at the UPMC Children's Hospital of Pittsburgh between 2010 and 2014. Patients were excluded if they had ESRD, baseline eGFR <15 ml/min per 1.73 m^2, or baseline serum creatinine ≥3.5 mg/dl, history of a renal transplant, ICU admission <60 minutes, stage 3 AKI on admission, age >18 years, or did not have sufficient information to categorize AKI status during days 3–8 of hospital stay. We also excluded patients who were given both TZP and cefepime within the first 2 days of ICU stay, given the risk of confounding with the primary medications being evaluated. Additionally, we excluded those who received sulfamethoxazole/trimethoprim because it can cause an artifactual increase in serum creatinine by inhibiting creatinine secretion in the proximal convoluted tubule. Other studies commonly exclude it as a nephrotoxin.[15,16]

Exposures

Primary exposures included each individual medication (vancomycin, TZP, and cefepime), as well as comparison of combination medications (vancomycin plus TZP [V+TZP] versus vancomycin plus cefepime [V+C]), administered within the first 48 hours of ICU admission. In the analyses assessing combination medications, patients in the cohort were designated as V+TZP or V+C if they received both vancomycin and TZP or vancomycin and cefepime, respectively, within the first 48 hours of ICU admission. This exposure window was chosen to reflect the time period when most children are placed on broad-spectrum antibiotics before antibiotic coverage is narrowed according to clinical evaluation.

Covariates

All parenteral or enteral antibiotics were included in the analysis, aside from erythromycin and neomycin, which are more often used for noninfectious indications in our ICU, and sulfamethoxazole/trimethoprim as described above (see Supplemental Table 1). Aside from antibiotics, additional nephrotoxic medications were accounted for if a patient was given three or more in the first 48 hours of ICU admission (see Supplemental Table 2).[16,17] Additional variables that have been associated with the development of AKI were included: age (universal covariate), history of heart failure, liver failure, CKD, malignancy, nonrenal transplant, epilepsy, congenital heart disease, electronic Pediatric Index of Mortality 2 score, abdominal compartment syndrome, vasopressor use, mechanical ventilation, suspected bacterial sepsis, thrombocytopenia, hypoalbuminemia, anemia, and major surgery.

Outcomes

The primary outcome was development of stage 2 or 3 AKI, or an increase in AKI stage from 2 to 3, within the 6 days after the 48-hour exposure window (*i.e.*, days 3–8). The primary exposure and outcome were designed to establish a temporal relationship between initial medication administration and subsequent development of AKI. AKI stage was defined using the Kidney Disease: Improving Global Outcomes criteria,[18] utilizing the maximum daily serum creatinine and/or a decrease in urine output over a 6-hour rolling window within the first 72 hours of ICU admission.[19] The

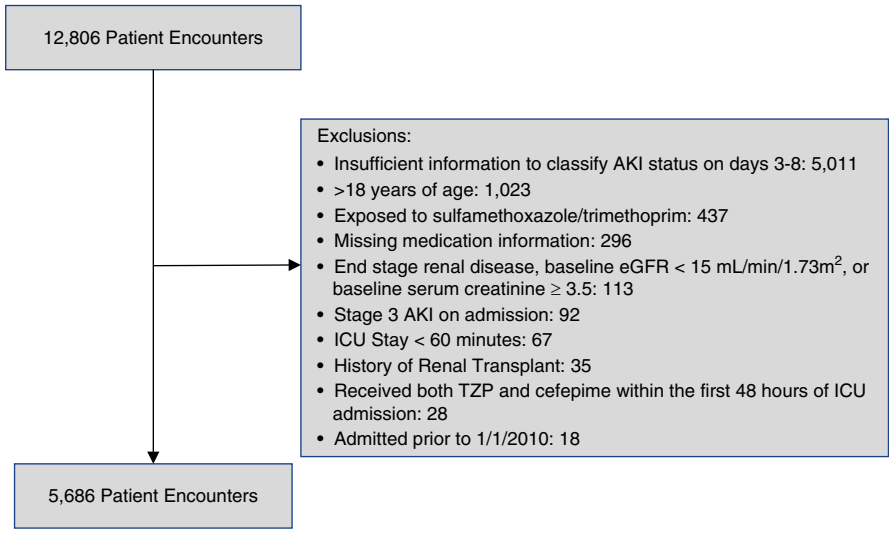

Figure 1. Flow diagram of study cohort with exclusions.

secondary outcomes were lengths of stay, need for RRT, and mortality.

Statistical Analyses

Statistical comparison of categorical and continuous variables were performed using chi-squared or Fisher exact tests and Wilcoxon rank-sum tests, respectively. For model development, all variables were assessed for univariate significance level of 0.2 followed by variable selection using LASSO regularization (least absolute shrinkage and selection operator). After clinical assessment in the final step, adjusted multivariable logistic regression for binary outcomes was performed to derive model inferences. All variables in the final model were considered significant at the 0.05 level. Model fit was tested using Hosmer–Lemeshow methodology[20] and discriminative ability (area under the curve [AUC] receiver operating curves). Secondary outcomes of mortality and need for RRT were assessed using univariate unadjusted logistic regression. For count data such as length of stay, zero-truncated negative binomial regression methods were applied and rate ratios were reported. For antibiotic combination analysis using propensity score matching, propensity score was generated while matching on baseline characteristics. We used 1:1 nearest neighbor matching between patients exposed to V+TZP and patients exposed to V+C. Variables included in the 1:1 matching were age, year of hospital admission, sex, race, history of heart failure, CKD, nonrenal transplant, malignancy, seizure/epilepsy, congenital heart disease, mechanical ventilation, major surgery, baseline serum creatinine, suspected bacterial sepsis, and use of vasopressors. Matches were created without replacement using computational geometry on the basis of distance between propensity scores (caliper 0.025). Conditional logistic regression was performed after propensity matching. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 15.1 (Stata Corp, College Station, TX).

RESULTS

A total of 5686 patient encounters were included in the analysis (Figure 1, Supplemental Table 3). Of these patient encounters, 494 (8.7%) developed stage 2 or 3 AKI in days 3–8 of hospital stay. There was no significant difference in age, sex, race, or year of admission between those who developed stage 2 or 3 AKI and those who did not (Table 1). Those who developed the primary outcome had a higher in-hospital mortality (5.9% versus 1.3%; $P<0.001$), longer ICU length of stay (8 days versus 4 days; $P<0.001$), and longer hospital admission (13 days versus 7 days; $P<0.001$).

Primary Outcome

Multivariable logistic regression that included individual antibiotic administration in the first 48 hours of admission showed good fit and reasonable discrimination (AUC, 0.71). A total of 1024 patients were exposed to TZP, 381 patients were exposed to cefepime, and 1902 patients were exposed to vancomycin. TZP (adjusted odds ratio [aOR], 1.56; 95% CI, 1.23 to 1.99) was associated with increased odds of developing stage 2 or 3 AKI or progression from stage 2 to stage 3 subsequent to administration (Table 2). Conversely, Cefepime was not associated with AKI (aOR, 1.13; 95% CI, 0.79 to 1.64), nor was vancomycin (aOR, 0.86; 95% CI, 0.69 to 1.07). The other individual antibiotics that remained in the adjusted model were levofloxacin, rifampin, and tobramycin, none of which were significantly associated with AKI.

Within the first 48 hours of ICU admission, there were 785 patient encounters exposed to V+TZP and 265 patient encounters exposed to V+C. For patients exposed to V+TZP, 16.7% developed AKI compared with 10.6% of the patients exposed to V+C ($P=0.02$). Patients who received V+TZP were younger (3.58 years versus 6.75 years; $P<0.001$), had higher prevalence

Table 1. Patient characteristics by AKI status

Characteristic	Maximum AKI Stage 0 or 1, *n*=5192 (91.3%)	Maximum AKI Stage 2 or 3, *n*=494 (8.7%)	*P* Value
Age (yr), median (Q1–Q3)	3.92 (1.08–11.17)	4.09 (0.92–12.17)	0.58
Males, *n* (%)	2965 (57.1%)	291 (58.9%)	0.44
Year of hospital admission			0.96
2010	805 (15.5%)	79 (16%)	
2011	977 (18.8%)	91 (18.4%)	
2012	1085 (20.9%)	107 (21.7%)	
2013	1151 (22.2%)	112 (22.7%)	
2014	1174 (22.6%)	105 (21.3%)	
Race, *n* (%)			0.83
White	4169 (80.8%)	399 (80.8%)	
Black	800 (15.4%)	72 (14.6%)	
Other	223 (4.4%)	23 (4.7%)	
Heart failure, *n* (%)	286 (5.5%)	57 (11.5%)	<0.001
Liver failure, *n* (%)	94 (1.8%)	26 (5.3%)	<0.001
Nonrenal transplant, *n* (%)	224 (4.3%)	22 (4.5%)	0.88
Malignancy, *n* (%)	338 (6.5%)	22 (4.5%)	0.07
Suspected bacterial sepsis within first 24 h of ICU admission, *n* (%)	1406 (27.1%)	196 (39.7%)	<0.001
CKD, *n* (%)	36 (0.7%)	13 (2.6%)	<0.001
Congenital heart disease, *n* (%)	914 (17.6%)	82 (16.6%)	0.57
Epilepsy/seizures, *n* (%)	1030 (19.8%)	134 (27.1%)	<0.001
Baseline serum creatinine, mean (SD)	0.37 mg/dl (0.22)	0.38 mg/dl (0.4)	0.62
Major surgery, *n* (%)	2219 (42.7%)	196 (39.7%)	0.19
Cardiopulmonary bypass, *n* (%)	565 (10.9%)	50 (10.1%)	0.60
Severe anemia, *n* (%)	849 (16.4%)	144 (29.1%)	<0.001
Thrombocytopenia, *n* (%)	1149 (22.1%)	211 (42.7%)	<0.001
Hypoalbuminemia, *n* (%)	1014 (19.5%)	199 (40.3%)	<0.001
Contrast exposure, *n* (%)	138 (2.7%)	21 (4.3%)	0.04
Exposure to ≥3 other nephrotoxins, *n* (%)	335 (6.5%)	45 (9.1%)	0.03
Vancomycin trough, mean (SD)[a]	8.41 mcg/ml (5.55)	10.04 mcg/ml (6.97)	<0.001
ePIM2 risk of mortality			
Median (Q1–Q3)	1% (0%–3%)	2% (1%–5%)	<0.001
Vasopressor use, *n* (%)	1345 (25.9%)	158 (32%)	0.003
Mechanical ventilation, *n* (%)			
Within first 24 h of ICU admission	2284 (44%)	311 (63%)	<0.001
Hospital mortality, *n* (%)	69 (1.3%)	29 (5.9%)	<0.001
Length of ICU stay in d, median (Q1–Q3)	4 (2–7)	8 (4–14)	<0.001
Length of hospital stay in d, median (Q1–Q3)	7 (5–13)	13 (8–22)	<0.001

Suspected bacterial sepsis: ordering of blood cultures and a new antibiotic within 24 hours of each other. Severe anemia: children aged <5 years, hemoglobin <7 g/dl on two consecutive occasions; children aged ≥5 years, hemoglobin <8 g/dl on two separate occasions. Thrombocytopenia: platelet count $<150\times10^9$/L on two consecutive occasions. Hypoalbuminemia: albumin level <3 g/dl on two consecutive occasions. Q, quartile; ePIM2, electronic Pediatric Index of Mortality 2.
[a]Mean vancomycin trough values are provided for those exposed to the medication.

of liver failure (3.9% versus 0.8%; P=0.01), lower prevalence of malignancy (5.5% versus 21.1%; P<0.001), were more likely to be suspected of bacterial sepsis (63.1% versus 54.7%; P=0.02), and had higher rates of mechanical ventilation within the first 24 hours of ICU admission (73% versus 52.5%; P<0.001) (Table 3). There was no difference in mean vancomycin trough levels between the two groups (9.31 versus 9.06; P=0.57). We found no statistical interaction between either of these two medication combinations, and the interaction terms did not modify the effect of individual drugs in the model.

Multivariable logistic regression was performed for exposure to V+TZP versus V+C, with subsequent development of stage 2 or 3 AKI or increase in AKI stage from 2 to 3, and showed good fit and discrimination (AUC, 0.70). In comparing V+TZP to V+C, the adjusted odds for development of AKI was not significant (aOR, 1.38; 95% CI, 0.85 to 2.24) (Table 4). Utilizing one-to-one propensity score matching, V+TZP showed an increased hazard for development of AKI (odds ratio [OR], 1.84; 95% CI, 1.11 to 3.05) compared with V+C (Supplemental Figure 1).

Secondary Outcomes

Patients who developed stage 2 or 3 AKI, compared with those who did not, had increased mortality (OR, 4.63; 95% CI, 2.97 to 7.22), increased need for RRT (OR, 18.46; 95% CI, 11.00 to

Table 2. Regularized multivariable logistic regression for development of stage 2 or 3 AKI, individual medications

Exposure	aOR (95% CI)	*P* Value
Cefepime, *n*=381	1.13 (0.79 to 1.64)	0.50
Levofloxacin, *n*=25	2.20 (0.65 to 7.46)	0.20
TZP, *n*=1024	1.56 (1.23 to 1.99)	<0.001
Rifampin, *n*=18	1.85 (0.54 to 6.34)	0.33
Tobramycin, *n*=180	1.30 (0.86 to 1.95)	0.21
Vancomycin, *n*=1902	0.86 (0.69 to 1.07)	0.18
Age[a]	1.03 (0.93 to 1.13)	0.61
Heart failure	1.48 (1.03 to 2.12)	0.03
Liver failure	1.40 (0.83 to 2.37)	0.20
CKD	2.06 (0.97 to 4.37)	0.06
Malignancy	0.54 (0.33 to 0.88)	0.01
Seizures/epilepsy	1.29 (1.04 to 1.61)	0.02
Major surgery	0.85 (0.70 to 1.05)	0.13
Severe anemia	1.53 (1.06 to 2.20)	0.02
Thrombocytopenia	1.65 (1.30 to 2.08)	<0.001
Hypoalbuminemia	1.33 (1.03 to 1.72)	0.03
Mechanical ventilation	1.52 (1.23 to 1.88)	<0.001
Exposure to ≥3 other nephrotoxins	1.35 (0.94 to 1.93)	0.10
Contrast exposure	1.21 (0.69 to 2.14)	0.50
Suspected bacterial sepsis	1.65 (1.21 to 2.24)	<0.001

[a]Age was standardized to its mean and SD.

30.97), and longer lengths of stay in the ICU (rate ratio, 2.11; 95% CI, 1.84 to 2.42) and hospital (rate ratio, 8.42; 95% CI, 5.90 to 10.94) (Table 5).

Patients exposed to TZP who developed stage 2 or 3 AKI, compared with those who did not develop AKI, had higher mortality (OR, 3.42; 95% CI, 1.53 to 7.69), increased need for RRT (OR, 7.08; 95% CI, 2.59 to 19.30), and longer lengths of stay in the ICU (rate ratio, 1.55; 95% CI, 1.26 to 1.90) and hospital (rate ratio, 1.40; 95% CI, 1.19 to 1.64). Patients exposed to vancomycin and V+TZP who developed stage 2 or 3 AKI similarly had higher mortality, higher need for RRT and longer lengths of stay (Table 5). In contrast, those exposed to cefepime who developed stage 2 or 3 AKI had increased need for RRT, but did not have statistically significant increase in mortality or longer lengths of stay. Lastly, patients exposed to V+C had increased ICU length of stay and need for RRT but no increase in hospital length of stay or mortality.

Additional Sensitivity Analyses

To further explore individual antibiotic exposure, an additional sensitivity analysis was performed to compare no AKI to stages 1, 2, or 3 AKI, and results remained consistent. Vancomycin and cefepime were not statistically significantly associated with any stage AKI, whereas TZP had an aOR of 1.70 (95% CI, 1.41 to 2.06) for development of any stage AKI (Supplemental Table 4). In another sensitivity analysis with the cohort limited to patients exposed to cefepime or TZP (*n*=1405), multivariable logistic regression showed a statistically insignificant adjusted odds of 1.34 (95% CI, 0.93 to 1.94) for development of stage 2 or 3 AKI with exposure to TZP compared with cefepime (Supplemental Table 5).

DISCUSSION

Nephrotoxic medication use is common in critically ill children,[8–10,21,22] and the effect on associated risk for developing AKI remains poorly understood. In addition to individual medications, coadministration of vancomycin and TZP is frequent in the pediatric critically ill population, particularly early in the course of ICU stay given the need for broad antibiotic coverage while evaluating a suspected bacterial infection. Adult and pediatric studies suggest that administration of vancomycin and TZP simultaneously confers an increased risk of AKI compared with vancomycin alone, TZP alone, and when compared with use of vancomycin and another β-lactam antibiotic.[8–14,22–27] Assessment of this medication combination has shown varying results in the critically ill population.[28–30] Our study is the largest to date that specifically evaluates the association between individual and concomitant administration of vancomycin, TZP, and cefepime with subsequent development of AKI in critically ill children (Figure 2).

Although other studies have generally looked at prolonged exposure to the medications of interest, we focused on exposure to antibiotics within the first 48 hours of ICU admission in an effort to examine the effect of the use of empiric antibiotic coverage (before a pathogen has been identified) on the association with subsequent development of AKI in days 3–8. This establishes the temporal relationship between exposure and outcome. A recent pediatric study retrospectively compared the risk of AKI with concomitant administration of vancomycin and TZP versus concomitant administration of vancomycin and another antipseudomonal β-lactam antibiotic.[9] Although this multicenter study had many strengths, only 30% of their patients required ICU-level care, and severity of illness was not captured. The results also grouped cefepime with meropenem, imipenem, and ceftazidime. We made a direct comparison between vancomycin with TZP and vancomycin with cefepime, so that an alternative to TZP is clearer when evaluating the risk for AKI.

Our analyses suggest that administration of TZP individually is associated with increased AKI risk in critically ill children. Exposure to TZP in the first 48 hours of ICU admission increased the odds of developing AKI in days 3–8 of hospitalization, with an aOR of 1.56 (95% CI, 1.23 to 1.99), whereas the other individual antibiotics did not reach statistical significance, which held true in a sensitivity analysis. In patients only exposed to TZP or cefepime, the adjusted odds of developing stage 2 or 3 AKI in those exposed to TZP alone compared with those exposed to cefepime alone was 1.34, but did not reach statistical significance

Table 3. Patient characteristics for combination medication exposure

Characteristic	Vancomycin+TZP, *n*=785	Vancomycin+Cefepime, *n*=265	*P* Value
Age (yr), median (Q1–Q3)	3.58 (1.33–10.42)	6.75 (2.33–12.75)	<0.001
Males, *n* (%)	433 (55.2%)	157 (59.2%)	0.25
Year of hospital admission			0.03
2010	150 (19.1%)	35 (13.2%)	
2011	183 (23.3%)	48 (18.1%)	
2012	161 (20.5%)	63 (23.8%)	
2013	148 (18.9%)	58 (21.9%)	
2014	143 (18.2%)	61 (23%)	
Race, *n* (%)			0.17
White	629 (80.1%)	212 (80%)	
Black	128 (16.3%)	37 (14%)	
Other	28 (3.6%)	16 (6%)	
Heart failure, *n* (%)	70 (8.9%)	16 (6%)	0.14
Liver failure, *n* (%)	31 (3.9%)	2 (0.8%)	0.01
Nonrenal transplant, *n* (%)	35 (4.5%)	19 (7.2%)	0.08
Malignancy, *n* (%)	43 (5.5%)	56 (21.1%)	<0.001
Suspected bacterial sepsis, *n* (%)			
Within first 24 h of ICU admission	495 (63.1%)	145 (54.7%)	0.02
CKD, *n* (%)	10 (1.3%)	7 (2.6%)	0.13
Congenital heart disease, *n* (%)	107 (13.6%)	29 (10.9%)	0.26
Epilepsy/seizures, *n* (%)	219 (27.9%)	62 (23.4%)	0.15
Baseline serum creatinine, mean (SD)	0.35 (0.29)	0.37 (0.28)	0.50
Major surgery, *n* (%)	212 (70%)	78 (29.4%)	0.44
Cardiopulmonary bypass, *n* (%)	30 (3.8%)	11 (4.2%)	0.81
Severe anemia, *n* (%)	204 (26%)	95 (35.8%)	0.002
Thrombocytopenia, *n* (%)	296 (37.7%)	117 (44.2%)	0.06
Hypoalbuminemia, *n* (%)	318 (40.5%)	83 (31.3%)	0.008
Contrast exposure, *n* (%)	36 (3.3%)	12 (4.5%)	0.36
Exposure to ≥3 other nephrotoxins, *n* (%)	60 (7.6%)	15 (5.7%)	0.28
ePIM2 risk of mortality median (Q1–Q3)	3.3% (1%–5%)	3.1% (1%–5%)	0.39
Vasopressor use, *n* (%)	252 (32.1%)	90 (34%)	0.58
Mechanical ventilation, *n* (%)			
Within first 24 h of ICU admission	573 (73%)	139 (34%)	<0.001
Need for RRT, *n* (%)	14 (1.8%)	6 (2.3%)	0.62
Hospital mortality, *n* (%)	20 (2.5%)	10 (3.8%)	0.3
Length of ICU stay in d, median (Q1–Q3)	6 (4–13)	5 (2–9)	<0.001
Length of hospital stay in d, median (Q1–Q3)	11 (6–21)	10 (6–17)	0.09
Vancomycin trough level, mean (SD)	9.31 (6.17)	9.06 (5.76)	0.57
Stage 2 or 3 AKI	131 (16.7%)	28 (10.6%)	0.02

Suspected bacterial sepsis: ordering of blood cultures and a new antibiotic within 24 h of each other. Severe anemia: children aged <5 years, hemoglobin <7 g/dl on two consecutive occasions; children aged ≥5 years, hemoglobin <8 g/dl on two separate occasions. Thrombocytopenia: platelet count $<150\times10^9$/L on two consecutive occasions. Hypoalbuminemia: albumin level <3 g/dl on two consecutive occasions. Q, quartile; ePIM2, electronic Pediatric Index of Mortality 2.

(*P*=0.12). Therefore, although TZP shows increased odds of AKI when used alone, there is not a clear benefit with regards to nephrotoxicity to use of cefepime over TZP individually.

Interestingly, although the rate of stage 2 or 3 AKI in the V+TZP group was higher at 16.7% compared with the V+C group at 10.6% (*P*=0.02), V+TZP versus V+C had an aOR of 1.38 for development of stage 2 or 3 AKI that did not reach statistical significance (*P*=0.19), similar to the findings reported by Schreier *et al.*[30] On the other hand, one-to-one propensity score matching showed an increased hazard of developing AKI when using V+TZP versus V+C (OR, 1.84; 95% CI, 1.11 to 3.05). Additionally, there was no statistical interaction observed between vancomycin and TZP in our analysis. Thus, although there is evidence of nephrotoxicity of TZP, with differing risk of AKI when assessing TZP individually versus in combination with vancomycin suggests ongoing uncertainty about a definitive association.

It is particularly interesting that vancomycin alone had adjusted odds for stage 2 or 3 AKI of 0.86 (95% CI, 0.69 to 1.07). We note, however, that vancomycin trough levels in our cohort averaged 9.18 mcg/ml, which is relatively low compared with adult populations, possibly explaining this lack of association. Other studies have suggested similar findings

Table 4. Regularized multivariable logistic regression for development of stage 2 or 3 AKI, medication combinations

Exposure	aOR (95% CI)	*P* Value
V+TZP versus V+C	1.38 (0.85 to 2.24)	0.19
Azithromycin, *n*=467	1.19 (0.74 to 1.93)	0.47
Cefazolin, *n*=1329	0.35 (0.10 to 1.20)	0.09
Doxycycline, *n*=23	3.48 (0.64 to 18.85)	0.15
Metronidazole, *n*=190	0.64 (0.28 to 1.48)	0.30
Age[a]	1.22 (0.99 to 1.52)	0.07
Heart failure	1.52 (0.80 to 2.88)	0.20
Liver failure	1.63 (0.62 to 4.27)	0.32
Malignancy	0.63 (0.28 to 1.40)	0.26
Seizures/epilepsy	1.49 (0.97 to 2.29)	0.07
Suspected bacterial sepsis	1.21 (0.55 to 2.65)	0.64
Major surgery	1.07 (0.63 to 1.81)	0.81
Cardiopulmonary bypass	2.24 (0.74 to 6.81)	0.15
Severe anemia	1.07 (0.66 to 1.74)	0.77
Thrombocytopenia	1.45 (0.93 to 2.27)	0.10
Hypoalbuminemia	1.33 (0.81 to 2.18)	0.26
ePIM2 score[a]	0.87 (0.66 to 1.14)	0.30
Vasopressors	1.20 (0.78 to 1.83)	0.41
Mechanical ventilation	2.42 (1.54 to 3.79)	<0.001

ePIM2, electronic Pediatric Index of Mortality 2.
[a]Age and ePIM2 score were standardized to their mean and SD.

with relative infrequency of AKI associated with vancomycin in pediatric patients, and often AKI is associated with exposure to multiple medications simultaneously.[31] In a subanalysis of critically ill adults, a meta-analysis showed that compared with vancomycin alone, V+TZP had an increased odds of AKI, but not when compared with V+C or TZP alone.[11] It is possible that vancomycin could play a role in impaired AKI recovery more so than development of AKI itself; the debate about nephrotoxicity of vancomycin remains ongoing.

Some authors have suggested that TZP has a pseudonephrotoxic effect with an increase in serum creatinine due to reduced creatinine secretion in the renal tubular organic anion transport system.[32] Disparate rates of AKI and the need for dialysis after exposure to TZP has supported this claim in another retrospective study of adult critically ill patients.[29] On the contrary, Ostermann *et al.*[33] has shown an increase in urinary biomarkers associated with renal tubular injury after exposure to TZP. Commensurate with the overall cohort that developed stage 2 or 3 AKI, exposure to TZP with subsequent development of stage 2 or 3 AKI is associated with longer lengths of stay, higher need for RRT, and increased mortality. Thus, our data suggest a potential true nephrotoxicity of TZP, although further research utilizing urinary biomarkers may provide clarity regarding renal stress after exposure to TZP.

There are limitations to our study, including that it is a single-center analysis with limited power. However, the frequency of severe AKI in our cohort is commensurate with the 11.6% of patients from the international Worldwide AKI, Renal Angina and, Epidemiology study.[1] We did not assess longer exposure to each antibiotic, nor were we able to classify all potential concurrent medication nephrotoxicities (*e.g.*, single nephrotoxic antibiotic with single additional nephrotoxic medication). Our analysis cohort excluded 5011 patients because of lack of data available to distinguish AKI in days 3–8 of the hospitalization, although is not entirely unexpected given the previously published relatively low rates of serum creatinine measurement between Pediatric Intensive Care Unit stay and hospital discharge.[34] Additionally, we cannot rule out indication bias contributing to the presented results and are limited by the nature of observational research. Lastly, it is important to note that we did not assess the potential side effects or detrimental outcomes that could be associated with using cefepime instead of TZP. These could include neurotoxicity in younger children as well as delayed coverage of anaerobic infections. Prospective studies could be helpful in deciphering the overall risk and benefit of using each of these antibiotics, and our data suggest the ongoing need for further analysis of TZP as a nephrotoxic medication in a robust manner with a potential future need for a randomized, controlled trial comparing TZP to cefepime.

Observational data in critically ill children show an association of TZP use with increased odds of AKI. A weaker, nonsignificant association is observed when TZP plus vancomycin is compared with cefepime plus vancomycin, resulting in residual uncertainty about whether the association of TZP with AKI reflects its use in a high-risk population. Cefepime is an alternative without association with AKI.

Table 5. Unadjusted secondary outcomes in patients with stage 2 or 3 AKI among cohorts of varying exposures

Exposure Cohort	Stage 2 or 3 AKI, *n* (%)	ICU LOS, rate ratio (95% CI)	Hospital LOS, rate ratio (95% CI)	Need for RRT, OR (95% CI)	Mortality, OR (95% CI)
Entire cohort, *n*=5686	494 (8.7%)	2.11 (1.84 to 2.42)[a]	8.42 (5.90 to 10.94)[a]	18.46 (11.00 to 30.97)[a]	4.63 (2.97 to 7.22)[a]
Cefepime, *n*=381	42 (11%)	1.48 (0.95 to 2.29)	1.17 (0.89 to 1.54)	5.82 (1.58 to 21.63)[a]	2.82 (0.74 to 10.86)
Vancomycin, *n*=1902	234 (12.3%)	1.63 (1.37 to 1.94)[a]	1.41 (1.23 to 1.57)[a]	17.23 (7.75 to 38.00)[a]	2.86 (1.55 to 5.28)[a]
TZP, *n*=1024	164 (16%)	1.55 (1.26 to 1.90)[a]	1.40 (1.19 to 1.64)[a]	7.08 (2.59 to 19.30)[a]	3.42 (1.53 to 7.69)[a]
V+TZP, *n*=785	131 (16.7%)	1.52 (1.22 to 1.91)[a]	1.42 (1.19 to 1.72)[a]	7.03 (2.40 to 20.60)[a]	2.78 (1.09 to 7.12)[a]
V+C, *n*=265	28 (10.6%)	1.87 (1.12 to 3.12)[a]	1.18 (0.85 to 1.64)	9.36 (1.80 to 48.90)[a]	3.95 (0.96 to 16.21)

LOS, length of stay.
[a]Values are statistically significant.

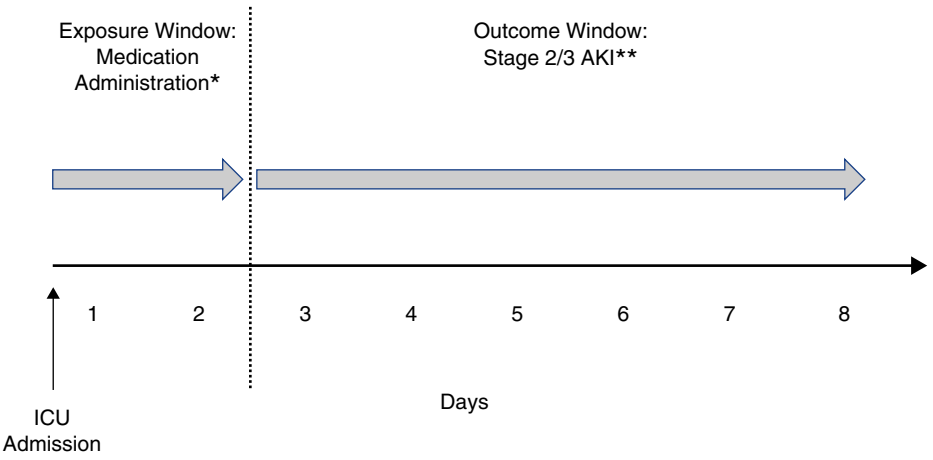

Figure 2. Schematic of primary analysis. *Medication exposure within the first 48 hours of admission; **AKI assessed as maximum AKI stage attained during days 3–8 of admission.

ACKNOWLEDGMENTS

We would like to thank the Biostatistical and Data Management Core within the CRISMA (Clinical Research Investigation and Systems Modeling of Acute Illness) Center for their help in variable development as well as data acquisition, management, and storage.

The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or UPMC Children's Hospital of Pittsburgh.

Dr. Joyce, Dr. Kane-Gill, Dr. Fuhrman, and Dr. Kellum designed the study; Ms. Priyanka analyzed the data; Dr. Joyce, Dr. Kane-Gill, Ms. Priyanka, and Dr. Kellum interpreted the data; Dr. Joyce, Dr. Kane-Gill, Dr. Fuhrman, Dr. Kellum, and Ms. Priyanka drafted and critically revised the manuscript; and all authors approved the final version of the manuscript.

DISCLOSURES

None.

FUNDING

This paper was supported by National Institutes of Health grant T32 DK091202 and the UPMC Children's Hospital of Pittsburgh Scholar Award Program.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2018121223/-/DCSupplemental.

Supplemental Table 1. List of antibiotics.

Supplemental Table 2. List of nephrotoxins (excluding antibiotics).

Supplemental Table 3. Characteristics of included versus excluded patient encounters.

Supplemental Table 4. Sensitivity analyses of individual medications, multivariable logistic regression for AKI.

Supplemental Table 5. Regularized multivariable logistic regression for development of stage 2 or 3 AKI in patients exposed to TZP versus cefepime.

Supplemental Figure 1. Love plot for absolute standardized differences of covariates before and after propensity score matching.

REFERENCES

1. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators: Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med* 376: 11–20, 2017
2. Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, et al.: Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med* 40: 1481–1488, 2014
3. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al.: AKI in hospitalized children: Comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol* 10: 554–561, 2015
4. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL: Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 71: 1028–1035, 2007
5. Bailey D, Phan V, Litalien C, Ducruet T, Mérouani A, Lacroix J, et al.: Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. *Pediatr Crit Care Med* 8: 29–35, 2007
6. Glanzmann C, Frey B, Vonbach P, Meier CR: Drugs as risk factors of acute kidney injury in critically ill children. *Pediatr Nephrol* 31: 145–151, 2016
7. Schneider J, Khemani R, Grushkin C, Bart R: Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. *Crit Care Med* 38: 933–939, 2010
8. McQueen KE, Clark DW: Does combination therapy with vancomycin and piperacillin-tazobactam increase the risk of nephrotoxicity versus vancomycin alone in pediatric patients? *J Pediatr Pharmacol Ther* 21: 332–338, 2016
9. Downes KJ, Cowden C, Laskin BL, Huang YS, Gong W, Bryan M, et al.: Association of acute kidney injury with concomitant vancomycin and piperacillin/tazobactam treatment among hospitalized children. *JAMA Pediatr* 171: e173219, 2017

10. Cook KM, Gillon J, Grisso AG, Banerjee R, Jimenez-Truque N, Phillips EJ, et al.: Incidence of nephrotoxicity among pediatric patients receiving vancomycin with either piperacillin-tazobactam or cefepime: A cohort study [published online ahead of print March 26, 2018]. *J Pediatric Infect Dis Soc* doi: 10.1093/jpids/piy030
11. Luther MK, Timbrook TT, Caffrey AR, Dosa D, Lodise TP, LaPlante KL: Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: A systematic review and meta-analysis. *Crit Care Med* 46: 12–20, 2017
12. Rutter WC, Burgess DR, Talbert JC, Burgess DS: Acute kidney injury in patients treated with vancomycin and piperacillin-tazobactam: A retrospective cohort analysis. *J Hosp Med* 12: 77–82, 2017
13. Mullins BP, Kramer CJ, Bartel BJ, Catlin JS, Gilder RE: Comparison of the nephrotoxicity of vancomycin in combination with cefepime, meropenem, or piperacillin/tazobactam: A prospective, multicenter study. *Ann Pharmacother* 52: 639–644, 2018
14. Giuliano CA, Patel CR, Kale-Pradhan PB: Is the combination of piperacillin-tazobactam and vancomycin associated with development of acute kidney injury? A meta-analysis. *Pharmacotherapy* 36: 1217–1228, 2016
15. Menon S, Kirkendall ES, Nguyen H, Goldstein SL: Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. *J Pediatr* 165: 522–527.e2, 2014
16. Moffett BS, Goldstein SL: Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. *Clin J Am Soc Nephrol* 6: 856–863, 2011
17. Sileanu FE, Murugan R, Lucko N, Clermont G, Kane-Gill SL, Handler SM, et al.: AKI in low-risk versus high-risk patients in intensive care. *Clin J Am Soc Nephrol* 10: 187–196, 2015
18. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). *Crit Care* 17: 204, 2013
19. Joyce EL, DeAlmeida DR, Fuhrman DY, Priyanka P, Kellum JA: eResearch in acute kidney injury: A primer for electronic health record research. *Nephrol Dial Transplant* 34: 401–407, 2019
20. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S: A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med* 16: 965–980, 1997
21. Slater MB, Gruneir A, Rochon PA, Howard AW, Koren G, Parshuram CS: Identifying high-risk medications associated with acute kidney injury in critically ill patients: A pharmacoepidemiologic evaluation. *Paediatr Drugs* 19: 59–67, 2017
22. Holsen MR, Meaney CJ, Hassinger AB, Fusco NM: Increased risk of acute kidney injury in critically ill children treated with vancomycin and piperacillin/tazobactam. *Pediatr Crit Care Med* 18: e585–e591, 2017
23. Abouelkheir M, Alsubaie S: Pediatric acute kidney injury induced by concomitant vancomycin and piperacillin-tazobactam. *Pediatr Int (Roma)* 60: 136–141, 2018
24. Burgess LD, Drew RH: Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. *Pharmacotherapy* 34: 670–676, 2014
25. 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. *Pharmacotherapy* 34: 662–669, 2014
26. LeCleir LK, Pettit RS: Piperacillin-tazobactam versus cefepime incidence of acute kidney injury in combination with vancomycin and tobramycin in pediatric cystic fibrosis patients. *Pediatr Pulmonol* 52: 1000–1005, 2017
27. Hundeshagen G, Herndon DN, Capek KD, Branski LK, Voigt CD, Killion EA, et al.: Co-administration of vancomycin and piperacillin-tazobactam is associated with increased renal dysfunction in adult and pediatric burn patients. *Crit Care* 21: 318, 2017
28. Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB: Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. *Clin Infect Dis* 64: 666–674, 2017
29. 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. *Pharmacotherapy* 36: 463–471, 2016
30. Schreier DJ, Kashani KB, Sakhuja A, Mara KC, Tootooni MS, Personett HA, et al.: Incidence of acute kidney injury among critically ill patients with brief empiric use of antipseudomonal β-lactams with vancomycin. *Clin Infect Dis* 68: 1456–1462, 2019
31. Moffett BS, Morris J, Kam C, Galati M, Dutta A, Akcan-Arikan A: Vancomycin associated acute kidney injury in pediatric patients. *PLoS One* 13: e0202439, 2018
32. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr T, Andersen MH, et al.: Procalcitonin And Survival Study (PASS) Group: Kidney failure related to broad-spectrum antibiotics in critically ill patients: Secondary end point results from a 1200 patient randomised trial. *BMJ Open* 2: e000635, 2012
33. Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, Shi J, et al.: All SAPPHIRE Investigators: Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. *Crit Care Med* 46: 375–383, 2018
34. Hessey E, Ali R, Dorais M, Morissette G, Pizzi M, Rink N, et al.: Renal function follow-up and renal recovery after acute kidney injury in critically ill children. *Pediatr Crit Care Med* 18: 733–740, 2017