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Incidence of Acute Kidney Injury Among Infants in the Neonatal Intensive Care Unit Receiving Vancomycin With Either Piperacillin/Tazobactam or Cefepime

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OBJECTIVES To determine whether combination therapy with vancomycin and TZP is associated with a higher incidence of acute kidney injury (AKI) compared with vancomycin with cefepime in infants admitted to the NICU.

METHODS This retrospective cohort study included infants in the NICU who received vancomycin/cefepime or vancomycin/TZP for at least 48 hours. The primary outcome was incidence of AKI, which was defined by the neonatal modified Kidney Disease Improving Global Outcomes AKI criteria.

RESULTS Forty-two infants who received vancomycin with cefepime and 58 infants who received vancomycin with TZP were included in the analysis. The median gestational age at birth, birth weight, and dosing weight were lower in the TZP group, but other baseline characteristics were comparable, including corrected gestational age. Two patients (3%) receiving vancomycin/TZP versus 2 patients (5%) receiving vancomycin/cefepime met criteria for AKI during their antibiotic course (p = 1.00). There were no clinically significant changes in serum creatinine or urine output from baseline to the end of combination antibiotic treatment in either group.

CONCLUSIONS Among infants admitted to our NICU, AKI incidence associated with vancomycin and either TZP or cefepime therapy was low and did not differ by antibiotic combination.

ABBREVIATIONS AKI, acute kidney injury; CHD, congenital heart disease; ICU, intensive care unit; NICU, neonatal intensive care unit; SCr, serum creatinine; TZP, piperacillin/tazobactam; UOP, urine output

KEYWORDS acute kidney injury; neonate; nephrotoxicity; piperacillin/tazobactam; vancomycin

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Introduction

Vancomycin is used in the NICU for treatment of Gram-positive microorganisms such as methicillin-resistant *Staphylococcus aureus*, coagulase-negative *Staphylococcus* species, and ampicillin-resistant *Enterococcus* species. Vancomycin is often administered in combination with cefepime or TZP to empirically treat patients with suspected serious bacterial infections. Although both cefepime and TZP are used for their broad Gram-negative coverage including activity against *Pseudomonas aeruginosa*, TZP additionally targets anaerobic microorganisms, and it is commonly used to treat complicated intra-abdominal infections.[1,2]

Nephrotoxicity is a well-established potential adverse effect of vancomycin. Vancomycin-induced nephrotoxicity has been associated with troughs above 15 mg/L and the concomitant use of other nephrotoxic drugs in children.[3–5] Specifically, the combination of vancomycin and TZP has been associated with an increased risk of acute kidney injury (AKI) in several studies of children and adults when compared with vancomycin monotherapy or vancomycin in combination with other β-lactam antibiotics such as cefepime.[6–11] In contrast, a few studies[12,13] did not find a significantly increased risk of AKI with vancomycin plus TZP versus cefepime, particularly in the critically ill adult population. Similar studies dedicated to infants in the NICU are lacking.

AKI in neonates is associated with poor outcomes, including mortality.[14] Although TZP is generally well tolerated with limited adverse effects in neonates, the incidence of AKI associated with TZP plus vancomycin combination therapy in this patient population is unknown.[15] Infants younger than 6 months of age were excluded from the largest published study in children that found an increased risk of AKI with the coadministration of vancomycin and TZP.[7] The purpose of this retrospective cohort study was to assess the incidence of AKI among infants who were admitted to the NICU and received vancomycin in combination with either cefepime or TZP.

Materials and Methods

This was a single-center, retrospective cohort study that compared the incidence of AKI among infants admitted to the NICU receiving vancomycin in combination with either cefepime or TZP for at least 48 hours between January 1, 2016, and October 29, 2018. This study was approved by the institutional review board at Vanderbilt University Medical Center. The NICU at Monroe Carell Jr. Children's Hospital at Vanderbilt is a level IV, 96-bed NICU. During the study period, vancomycin was dosed using an institution-specific ordering panel within the electronic medical record.

Patients were included if they were admitted to the NICU, administered at least 48 hours of combination antibiotic therapy (vancomycin plus either cefepime or TZP), and had at least 1 serum creatinine (SCr) or urine output (UOP) measurement documented at baseline and at the end of the antibiotic course. Combination antibiotic courses were included when drugs were coadministered for at least 48 hours; individual antibiotics were not always initiated within the same day. Patients were excluded if they had a history of structural kidney disease, received dialysis at the initiation of the treatment course, or were supported with extracorporeal membrane oxygenation during the treatment course. Patients were also excluded if they experienced AKI within 24 hours prior to the start of combination antibiotic therapy. Multiple courses of combination antibiotic therapy per patient were included if the courses were at least 2 weeks apart.

The primary outcome was incidence of AKI for patients receiving vancomycin with either cefepime or TZP. Secondary outcomes included change in SCr and change in UOP from the start to the end of combination antibiotic treatment. Acute kidney injury was defined using the most updated version of the neonatal modified Kidney Disease Improving Global Outcomes AKI definition (2016 modification), which includes criteria based on changes in either SCr or UOP. Stage 1 AKI is defined by a rise in SCr of at least 0.3 mg/dL within 48 hours, SCr at least 1.5 to 1.9 times the previous lowest value within 7 days, or UOP less than or equal to 1 mL/kg/hr for 24 hours. Stage 2 AKI is defined by a rise in SCr of at least 2 to 2.9 times the baseline or UOP less than 0.5 mL/kg/hr for 24 hours. Stage 3 AKI is defined by a rise in SCr of at least 3 times the baseline, a SCr of at least 2.5 mg/dL, initiation of renal replacement therapy, or UOP <0.3 mL/kg/hr for 24 hours.[16]

Baseline SCr in this study was defined as the SCr on the first day of combination antibiotic therapy or the most recent SCr within 7 days prior. All available SCr measurements obtained during administration of combination antibiotics were collected. Baseline UOP was the patient's 24-hour UOP on the day that combination antibiotic therapy was started. Urine output was then collected for each 24-hour period (7:00 am to 7:00 am the next day) during combination antibiotic therapy. Concomitant nephrotoxic agents, including aminoglycosides, acyclovir, angiotensin-converting enzyme inhibitors, amphotericin B, loop diuretics, nonsteroidal anti-inflammatory drugs, radiocontrast agents, and vasopressors, were collected if the patient was administered at least 1 dose while receiving combination antibiotic therapy. Antibiotic indications, doses, and vancomycin levels were recorded. Positive cultures within 24 hours prior to or during antibiotic therapy were also collected.

Descriptive analyses were reported as median (range) for continuous variables and frequency (percentage) for categorical data. Baseline characteristics and outcomes were evaluated using the Wilcoxon rank sum test for continuous variables and the Pearson c^2 test or Fisher exact test, as appropriate, for categorical variables. To analyze the difference in SCr and UOP from baseline to end of course, the sign test of equality of matched pairs was used. Data were analyzed using Strata 14.2 (StrataCorp, LP, College Station, TX).

Results

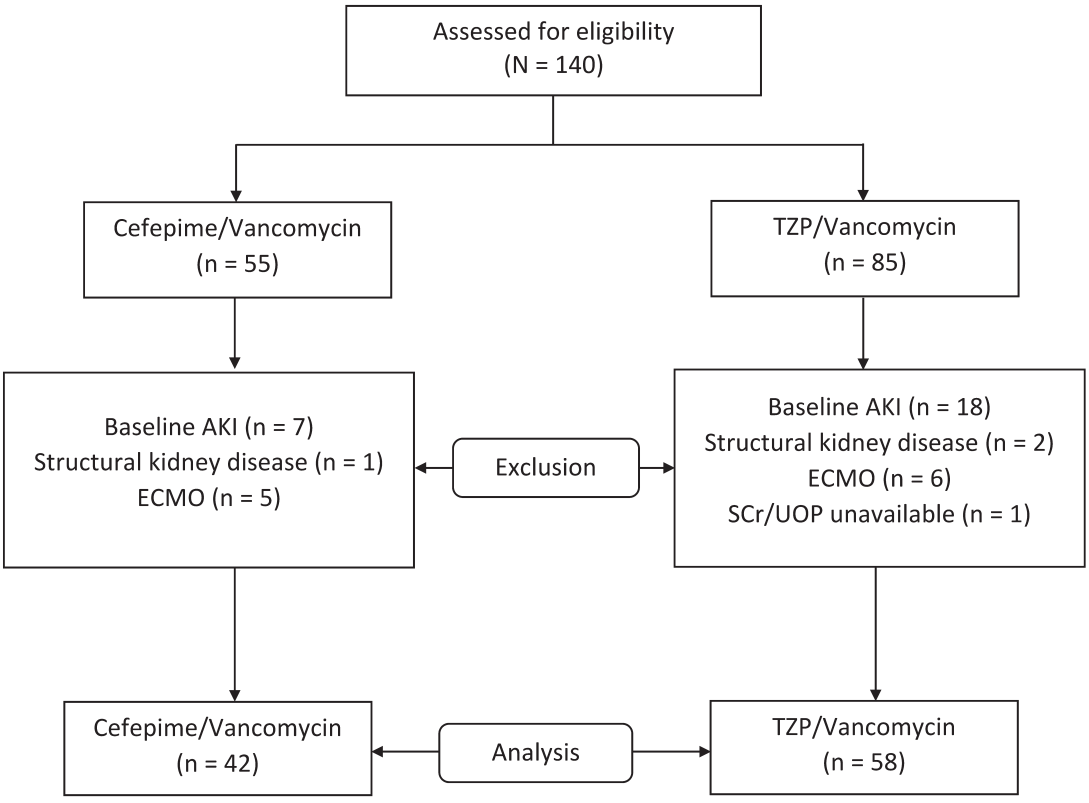
A total of 140 antibiotic courses were reviewed for inclusion. Reasons for exclusion are displayed in Figure 1. Ultimately, 42 infants who received vancomycin with cefepime and 58 infants who received vancomycin with TZP were included in the analysis. Eight patients were included more than once because they received multiple combination antibiotic courses that were at least 2 weeks apart (7 patients were included twice and 1 patient was included 3 times).

Baseline patient characteristics are summarized in Table 1. The vancomycin/TZP group had a significantly lower gestational age at birth, birth weight, and dosing weight. All other baseline characteristics were similar between groups. Approximately 81% of infants receiving vancomycin/cefepime and 90% of infants receiving vancomycin/TZP were a postmenstrual age of 44 weeks or less at the start of antibiotic therapy (range 24 to 60 weeks).

Characteristics of the antibiotic courses are summarized in Table 2. The median duration of combination antibiotic therapy was 3.5 days. The majority of patients in both groups were on concomitant nephrotoxic agents. Approximately 40% of patients in the vancomycin/TZP group were being treated for an intra-abdominal infection, whereas no patient in the vancomycin/cefepime group received antibiotics for this indication. The vancomycin total daily dose was similar in both groups, with a median of 30 mg/kg/day. The most common cefepime and TZP doses were 50 mg/kg/dose every 8 hours and 100 mg piperacillin/kg/dose every 8 hours, respectively.

Only 2 patients (5%) receiving vancomycin/cefepime and 2 patients (3%) receiving vancomycin/TZP met the criteria for AKI during their antibiotic course (p = 1.00). Table 3 provides details regarding the characteristics of these 4 patients. All 4 patients were receiving additional

Figure. Patient inclusion and exclusion.



AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; SCr, serum creatinine; UOP, urine output

nephrotoxic medications. Three of the patients received multiple doses of furosemide, and 2 of the patients received gentamicin and infusions of vasopressors. Diagnosis of AKI was Stage 1 based on SCr criteria alone for all 4 patients; no patient had a 24-hour UOP less than 1 mL/kg/hr during combination antibiotic therapy or required renal replacement therapy.

There were no clinically significant changes in median SCr or UOP from baseline to the end of treatment in either group. In the patients receiving vancomycin/cefepime, the median SCr was 0.42 mg/dL both at baseline and at the end of treatment ($p = 0.05$), and the median UOP was 4.0 mL/kg/hr at baseline and 4.5 mL/kg/hr at the end of treatment ($p = 0.28$). In the patients receiving vancomycin/TZP, the median SCr was 0.48 mg/dL and 0.45 mg/dL at the beginning and end of treatment, respectively ($p = 0.005$). The median UOP was 3.7 mL/kg/hr and 3.9 mL/kg/hr at the beginning and end of treatment, respectively ($p = 0.10$).

Discussion

In this retrospective study of 100 infants in the NICU receiving either vancomycin with cefepime or vancomycin with TZP, we found a low and similar incidence of AKI among patients receiving both combinations of antibiotics. Only 4% of the entire cohort (2 with vancomycin/cefepime and 2 with vancomycin/TZP) met the criteria for Stage 1 AKI during treatment. The changes in SCr and UOP from baseline to the end of treatment were not deemed clinically significant in either group. To our knowledge, this is the first study to examine the incidence of nephrotoxicity with the combination of vancomycin and TZP in a largely neonatal population.

The 4 patients who experienced nephrotoxicity in our study had common characteristics that might have predisposed them to AKI. Three of the 4 patients had congenital heart disease (CHD), which might have predisposed them to poor renal perfusion. All 4 patients had positive cultures (1 bronchoalveolar, 1 blood, and 2 tracheal cultures), thus infection or sepsis might have decreased renal perfusion. These patients also had a longer duration of combination antibiotic therapy compared with the median duration of the entire cohort (7 days versus 3.5 days). Additionally, these patients all received concomitant nephrotoxic medications, includ-

Table 1. Baseline Patient Characteristics

	Total (N = 100)	Cefepime/Vancomycin (n = 42)	TZP/Vancomycin (n = 58)	p value
Gestational age at birth, median (range), wk	29 (22–42)	33 (23–42)	27 (22–39)	0.029*
Birth weight, median (range), g	1235 (385–4283)	1770 (430–4283)	980 (385–3912)	0.028*
Male, n (%)	56 (56)	22 (52)	34 (59)	0.54†
CHD, n (%), present	17 (17)	8 (19)	9 (16)	0.64†
Age at antibiotic start, median (range), days	24 (1–235)	23 (3–173)	25 (1–235)	0.85*
Corrected gestational age at antibiotic start, median (range) wk	35 (24–60)	37 (26–58)	33 (24–60)	0.089*
Dosing weight at start date, median (range), kg	2.1 (0.5–6.8)	2.5 (0.6–5.5)	2.0 (0.5–6.8)	0.038*
Baseline SCr, median (range), mg/dL	0.47 (0.24–1.09)	0.42 (0.28–0.93)‡	0.48 (0.24–1.09)§	0.55*
Baseline UOP, median (range), mL/kg/hr	3.8 (1.5–6.7)	4.0 (1.6–5.5)	3.7 (1.5–6.7)¶	0.63*

CHD, congenital heart disease; SCr, serum creatinine; UOP, urine output

* Wilcoxon rank sum test.

† Pearson c^2 test.

‡ n = 39.

§ n = 57.

¶ n = 55.

ing furosemide, gentamicin, and vasopressors during combination antibiotic therapy. Interestingly, the lowest 24-hour UOP for each patient remained within a normal range (2.2 to 3.3 mL/kg/hr). For patients 1 and 4 in which antibiotics were continued for a few more days after the increase in SCr, the UOP remained adequate and antibiotics were not dose-adjusted. Patient 1 did not have a repeat vancomycin trough, and patient 4 had a vancomycin trough of 14 mg/L on the day of their highest SCr level.

A strength of this retrospective study included the collection of daily UOP documentation, which is a valuable indicator of renal function that has not been reported in other pediatric studies assessing the risk of AKI with these antibiotic combinations. Although SCr is the standard measurement used for the diagnosis of AKI in most studies, there is a delay in the rise of SCr after a decrease in renal function. In addition, the use of SCr as a marker of renal dysfunction in neonates has distinct challenges such as the presence of maternal creatinine, overall lower glomerular filtration rates, and varying degrees of creatinine reabsorption.[14] SCr and UOP were documented in 90% and 97% of patients, respectively, at both baseline and end of course. The majority of patients also had daily UOP documented in the medical record. The timing of antibiotic therapy and SCr measurements were carefully noted, and patients were excluded if they met criteria for AKI prior to starting combination antibiotic therapy. Because sepsis has consistently been shown to be a risk factor for the development of AKI in neonates, it was prudent to exclude patients who developed AKI on the same day as starting empiric antibiotics to reduce the effect of this confounding variable.[14]

Limitations of this study include those inherent to retrospective chart review studies, including reliance on accurate documentation in the medical record. It is possible, given the retrospective design, that additional confounding variables existed that were not accounted for (i.e., severity of illness score or fluid status) and that might have influenced the risk of AKI. The sample size was small, so the study may not have been sufficiently powered to detect a difference in AKI, which was a rare outcome. Characteristics including gestational age at birth, birth weight, and indication for antibiotics differed between the groups. On one hand, compared with the vancomycin/cefepime group, the vancomycin/TZP group was more preterm, smaller, and had more intra-abdominal infections; these conditions should have biased toward detection of more AKI in these infants, which we did not observe. On the other hand, more patients in the vancomycin/cefepime group were being treated for bacteremia or meningitis; they received vancomycin every 6 hours, which might indicate a higher severity of infection in this group. The treatment groups were not matched for possible confounders because this would have significantly reduced the sample size. The median duration of combination antibiotic therapy was 3.5 days in our study, so we could not evaluate if longer courses of therapy are associated with AKI. Due to the low incidence of AKI in both groups, we were unable to perform multivariable analysis to assess for risk factors of nephrotoxicity.

There are several studies that have observed an association between AKI and concomitant vancomycin and TZP treatment in children and adults.[6–11] A meta-analysis[6] including 14 observational studies (including 3 studies with children) totaling 3549 patients compared

Table 2. Antibiotic Course Characteristics

	Cefepime/Vancomycin (n = 42)	TZP/Vancomycin (n = 58)	p value
Duration of combination therapy, median (range), days	3.7 (2.0–13.4)	3.3 (2.0–12.0)	0.88*
Concomitant nephrotoxins, n (%)			0.62†
None	16 (38)	25 (43)	
Aminoglycoside	3 (7)	2 (3)	
Acyclovir	4 (10)	1 (2)	
Loop diuretic	15 (36)	23 (40)	
NSAID	0 (0)	1 (2)	
Radiocontrast agent	1 (2)	1 (2)	
Sirolimus	1 (2)	0 (0)	
Vasopressor	10 (24)	12 (21)	
Positive culture, n (%)	22 (52)	24 (41)	0.28†
Indication,‡ n (%)			
Empiric for sepsis	19 (45)	23 (40)	
Bacteremia	6 (14)	3 (5)	
Intra-abdominal infection	0 (0)	24 (41)	
Pneumonia	8 (19)	5 (9)	
Meningitis	5 (12)	0 (0)	
UTI	3 (7)	4 (7)	
Tracheitis	6 (14)	1 (2)	
SSTI	4 (10)	4 (7)	
Vancomycin dosing, median (range), mg/kg/ day	30 (20–60)	30 (20–60)	0.55*
Vancomycin frequency, n (%)			0.12§
Every 6 hr	5 (12)	1 (2)	
Every 8 hr	33 (79)	49 (84)	
Every 12 hr	4 (9)	8 (14)	
First steady-state vancomycin trough, median (range), mg/mL	8 (3–20)	11 (3–26)	0.58*
Vancomycin trough >20 mg/L during treatment, n (%)	1 (2)	3 (5)	0.64§
Cefepime dosing, median (range), mg/kg/dose	50 (48–54)	N/A	
Cefepime frequency, n (%)		N/A	
Every 8 hr	32 (76)		
Every 12 hr	10 (24)		
TZP dosing, median (range), mg/kg/dose	N/A	100 (52–105)	
TZP, frequency, n (%)	N/A		
Every 6 hr		3 (5)	
Every 8 hr		44 (76)	
Every 12 hr		11 (19)	

NSAID, nonsteroidal anti-inflammatory drug; SSTI, skin or soft tissue infection; UTI, urinary tract infection

* Wilcoxon rank sum test.

† Pearson c^2 test.

‡ Multiple indications were allowed per course.

§ Fisher exact test.

the incidence of AKI with concomitant vancomycin and TZP versus vancomycin monotherapy or in combination with any other β-lactam antibiotic. Vancomycin in combination with TZP was associated with an increased risk of AKI in analyses for both adults and pediatric patients (adjusted odds ratio, 3.11; 95% CI, 1.77–5.47). This relationship was not found when an adjusted analysis was restricted to studies with greater than 50% of patients in the ICU; it may be a result of the ICU population already having an increased baseline risk of AKI independent of vancomycin and TZP exposure.

A large, retrospective cohort study using the Pediatric Health Information System Plus database assessed the risk of AKI in 1915 hospitalized children, of which 1009 (53%) received vancomycin plus TZP and 422 (22%) received vancomycin plus cefepime. The cumulative incidence of antibiotic-associated AKI was 11.7% in patients receiving vancomycin and TZP and 4% in patients receiving vancomycin and cefepime. Vancomycin plus TZP was associated with higher odds of AKI compared with vancomycin plus one other β-lactam antibiotic after adjustment for age, ICU level of care, and receipt

Table 3. Characteristics of Patients With Acute Kidney Injury

	Patient 1	Patient 2	Patient 3	Patient 4
Cohort	TZP	TZP	Cefepime	Cefepime
Gestational age at birth, wk	38	31	33	23
Age at the start of antibiotics, days	104	44	15	71
Corrected gestational age at the start of antibiotics, wk	52	37	35	33
CHD	Yes	Yes	No	Yes
Duration of treatment, days	7.0	7.0	6.4	7.7
Supratherapeutic vancomycin troughs	No	No	Yes (21 mg/L)	No
Concomitant nephrotoxins	Furosemide	Furosemide	Gentamicin Furosemide Epinephrine	Gentamicin Epinephrine Dopamine
Time to AKI, days	2.9	6.2	4.4	1.6
Largest increase in SCr, mg/dL	0.48→0.76	0.49→0.80	0.35→0.60	0.38→0.58
Lowest UOP over 24 hr, mL/kg/hr	3.3	2.2	2.6	2.8

AKI, acute kidney injury; CHD, congenital heart disease; SCr, serum creatinine; UOP, urine output

of nephrotoxins (adjusted odds ratio, 3.40; 95% CI, 2.26–5.14). However, this potential risk of combination therapy should not be extrapolated to the neonatal population based on this study because they excluded patients younger than 6 months of age.[7]

Cook et al[8] also found an increased incidence of AKI with the vancomycin/TZP combination (28.9%) versus vancomycin/cefepime combination (7.9%) in a retrospective matched-cohort study of 228 pediatric patients. An exceptionally high rate of AKI with vancomycin/TZP was seen in patients with CHD (47.9%), but it is unknown how many were also receiving additional nephrotoxins because these patients commonly receive loop diuretics. This study included patients < 18 years of age but did not report the number of neonates included in the study nor the incidence of AKI with these antibiotic combinations in the neonatal population. Similar to previous studies, AKI was diagnosed by SCr alone because UOP information was not collected. In addition, 11 of the 42 patients who experienced AKI had an elevated SCr within 1 calendar day after the initiation of their combination antibiotic therapy.[8] In contrast, the previously described Pediatric Health Information System Plus database study excluded AKI identified on days 0 to 2.[7] This exclusion might partly explain the higher incidence of AKI with both antibiotic combinations in the study by Cook et al.[8]

A low incidence of antibiotic-associated AKI may be unique to neonates. Other studies have also found an infrequent occurrence of AKI in neonates treated with supposed nephrotoxic antibiotic combinations. In a retrospective propensity-score matched cohort study comprising 1066 neonates, AKI occurred in 3% of patients receiving vancomycin with gentamicin and 1.3% of patients receiving gentamicin alone. Nephrotoxicity risk factors included a patent ductus arteriosus, concomitant nonsteroidal anti-inflammatory medications, at least 1 positive blood culture, low birth weight, and higher severity of illness; however, vancomycin use was not associated with AKI.[17] Nephrotoxicity associated with amphotericin B deoxycholate is also known to be considerably less in neonates than in older children and adults.[18,19] Why neonates experienced less nephrotoxicity following exposure to nephrotoxic medications is unclear.

Defining AKI in neonates is complex due to a variety of factors, including the presence of maternal creatinine and changes in renal blood flow and tubular function over time. Because of these physiologic changes and the decline of SCr postnatally, there is not a true "baseline steady-state SCr" in neonates.[16] It is uncertain whether using SCr and/or UOP is the best way to identify acute renal impairment in the neonatal population, and it is possible that AKI may be underdiagnosed by using these criteria. Using the neonatal modified Kidney Disease Improving Global Outcomes AKI criteria moving forward will provide consistency across studies, but this definition still requires validation and evaluation in large multicenter studies.

Conclusion

Infants in our NICU receiving combination antibiotics for a short duration had a low incidence of AKI, and AKI rates did not differ between those receiving vancomycin with either TZP or cefepime. This study suggests that neonates may be less susceptible to vancomycin plus TZP induced nephrotoxicity as compared with children and adults. Larger trials are necessary to validate this observation.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. Given the nature of the study, institutional review board/ethics committee review was not required and informed consent was waived.

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