CASE REPORT

Acute Kidney Injury in a Child Receiving Vancomycin and Piperacillin/Tazobactam

Bethany W. Ibach, PharmD,[1] Emilie D. Henry, MD,[2] and Peter N. Johnson, PharmD[3]

[1]Texas Tech University Health Sciences Center School of Pharmacy, Abilene, Texas; [2]University of Oklahoma College of Medicine, Oklahoma City, Oklahoma; [3]University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma

Recent reports have described increased risk of acute kidney injury (AKI) in adults receiving concomitant vancomycin and piperacillin/tazobactam, but few reports exist in children. We describe an 8-year-old girl who was admitted to the pediatric intensive care unit with respiratory distress secondary to pneumonia. She began treatment with vancomycin and piperacillin/tazobactam. She developed AKI, and piperacillin/tazobactam and vancomycin were discontinued. Following a furosemide infusion, her AKI resolved and serum creatinine returned to baseline. She later resumed piperacillin/tazobactam monotherapy for multidrug-resistant tracheitis with no evidence of AKI and was eventually discharged to a long-term care facility. The Naranjo probability scale supports a probable drug-related adverse event. Clinicians must be aware of the possibility of AKI with this combination and should monitor renal function and vancomycin concentrations vigilantly. Future prospective studies are needed to explore the incidence and clinical characteristics associated with AKI after this combination in children.

INDEX TERMS: acute kidney injury, child, piperacillin/tazobactam, vancomycin

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INTRODUCTION

Vancomycin and piperacillin/tazobactam can be used as monotherapy or in combination for infections in critically ill children. Recent reports have suggested increased rates of acute kidney injury (AKI) in adults receiving this combination compared with vancomycin monotherapy.[1–7] However, few reports of this adverse event exist in children. This case report describes a child who developed AKI and subsequent fluid overload with concomitant vancomycin and piperacillin/tazobactam therapy.

CASE REPORT

An 8-year-old girl (29.9 kg, 122 cm), with a medical history that included cerebral palsy, tracheal stenosis after resection, epilepsy, microcephalus, congenital hypothyroidism, obstructive sleep apnea, and gastrostomy-tube dependence, was transferred from a long-term care (LTC) facility with acute respiratory distress. Two days before admission, she developed fever, increased work breathing, and hypoxemia requiring supplemental oxygen of 5 to 6 L/min by face mask. A chest radiograph at the LTC facility was suggestive of left-sided pneumonia, and her respiratory panel was positive for parainfluenza. Treatment was initiated with ceftriaxone, but her respiratory status continued to worsen, so she was transferred for further care.

Upon admission to the emergency department, her temperature was 38.4°C, pulse 153 beats/min, respiratory rate 24 breaths/min, blood pressure 106/40 mm Hg, and oxygen saturation 93% on 8 L/min by face mask. Significant findings on physical exam included copious dark brown secretions, crackles, cough, and decreased left-sided breath sounds. A chest radiograph showed consolidation that had progressed to include the entire left lung and lower lobe of the right lung. Table 1 provides her admission laboratory values. Her complete metabolic panel was within reference range, including a baseline serum creatinine (SCr) of 0.31 mg/dL and blood urea nitrogen (BUN) of 7 mg/dL. She had a white blood cell (WBC) count of 13,600/mm^3 with 81%

Table 1. Selected Chemistry and Hematology Values on Admission

Parameter (Reference Range)	Patient Value
Sodium (134-144 mEq/L)	142
Potassium (3.5-5.1 mEq/L)	4.5
Chloride (96-108 mEq/L)	99
Carbon dioxide (22-30 mEq/L)	36
BUN (7-18 mEq/L)	7
Creatinine (0.2-0.7 mg/dL)	0.31
Glucose (65-110 mg/dL)	93
Procalcitonin (ng/mL)	0.52
CRP (mg/L)	200.3
WBC (4.5-13.5 K/mm^3)	13.6
Hemoglobin (10.9-14.9 g/dL)	11.4
Hematocrit (30.5%-44.5%)	34.4
Platelets (150-400 K/mm^3)	263

BUN, blood urea nitrogen; CRP, C-reactive protein; WBC, white blood cells

neutrophils and 6% bands. Her C-reactive protein (CRP) and procalcitonin were elevated (Table 1). A blood culture was positive for coagulase-negative *Staphylococcus* in 1 of 2 bottles. However, this was considered a contaminant. She received a 20 mL/kg bolus of normal saline and one intravenous (IV) dose each of piperacillin/tazobactam (84 mg/kg; piperacillin component) and vancomycin (18.5 mg/kg).

She was transferred to the pediatric intensive care unit (PICU) for further care. At this time, her calculated Pediatric Risk of Mortality III score was 5. In the PICU, she was continued on oxygen by face mask. Table 2 provides an overview of her antibiotic exposure during hospital days (HDs) 1 to 12 in the PICU. She was initiated on ceftriaxone at 67 mg/kg/dose IV every 24 hours and vancomycin 18.5 mg/kg/dose IV every 8 hours, with a target trough concentration of 15 to 20 mg/L (Table 2). On HD 2, because of worsening clinical status, she was transitioned to bilevel positive airway pressure (BiPAP), and her ceftriaxone was discontinued and replaced with piperacillin/tazobactam at 100 mg/kg/dose IV every 8 hours because of concerns for nosocomial pneumonia with *Pseudomonas aeruginosa*. A repeat blood culture was negative. Her vancomycin dose was increased to 18.5 mg/kg/dose IV every 6 hours after her trough concentration was reported to be <5 mg/L.

On HD 3, she continued to have signs of increased respiratory distress with BiPAP and was initiated on additional respiratory therapies, including cough assist every 4 hours, 3% sodium chloride solution nebulized every 4 hours, and albuterol nebulized every 4 hours as needed. Her repeat procalcitonin was 41.92 ng/mL, and CRP was 355.1 mg/L. A third blood culture was analyzed, and a urine culture was obtained; however, these were both negative. Her piperacillin/tazobactam dose was optimized to 100 mg/kg/dose IV every 6 hours. A repeat vancomycin trough was checked before the third dose of her new regimen and was 17 mg/L, so this dose was continued without further changes.

On HD 4, her urinary output (UOP) decreased significantly, and her SCr increased to 1.16 mg/dL (374% increase from baseline) with a glomerular filtration rate of 57.8 mL/min/1.73 m^2 as calculated by the bedside Swartz equation (Table 3) (Figure).[8] This corresponded to a 73% decrease in estimated glomerular filtration rate and was classified as AKI based on the pediatric-modified RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria.[9] A urinalysis revealed 1$^+$ protein but no eosinophils or casts. The follow-up vancomycin trough concentration on HD 4 was 37 mg/L. At that time, vancomycin and piperacillin/tazobactam were discontinued because of concerns for AKI. Her antibiotics were changed to IV azithromycin and ceftriaxone (Table 2). No additional nephrotoxic agents were identified. She was given a single dose of IV furosemide (0.3 mg/kg) and 25% albumin (1 g/kg) to augment her UOP. By HD 5, she had a cumulative 18.3% positive fluid balance (5.5 L positive result) and was initiated on a furosemide continuous infusion at 0.05 mg/kg/hr (Table 3). Her follow-up vancomycin concentration was 5 mg/L approximately 36 hours after her last dose. On HD 6, she had progressive hypercarbia and acute respiratory distress syndrome (ARDS), and she was intubated and placed on mechanical ventilation.

During the next several days, her renal function improved. Her furosemide continuous infusion was discontinued on HD 10; at which time, her cumulative fluid balance was improved to 5.8%

Table 2. Antibiotic Therapy During Intensive Care Unit Admission from Hospital Days 1 to 12

HD	Azithromycin	Ceftriaxone	Piperacillin/ Tazobactam,*	Vancomycin	Ceftazidime
1	—	67 mg/kg q 24 hr	84 mg/kg PIP x 1 dose	18.5 mg/kg q 8 hr	—
2	—	Discontinued	100 mg/kg PIP q 8 hr	18.5 mg/kg q 6 hr	—
3	—	—	100 mg/kg PIP q 6 hr	18.5 mg/kg q 6 hr	—
4	5 mg/kg q 24 hr	67 mg/kg q 24 hr	Discontinued	Discontinued	—
5	5 mg/kg q 24 hr	67 mg/kg q 24 hr	—	—	—
6	5 mg/kg q 24 hr	67 mg/kg q 24 hr	—	—	—
7	5 mg/kg q 24 hr	67 mg/kg q 24 hr	—	—	—
8	5 mg/kg q 24 hr	67 mg/kg q 24 hr	—	—	—
9	Discontinued	67 mg/kg q 24 hr	—	—	—
10	—	Discontinued	—	—	—
11	—	—	—	—	50 mg/kg q 8 hr
12	—	—	—	—	Discontinued

HD, hospital day; PIP, pipericillin
* Dosing calculated via the piperacillin component

(1.7 L positive result) (Table 3) (Figure). Her azithromycin was completed on HD 9, and her ceftriaxone was discontinued on HD 10. She continued to receive diuresis with intermittent IV furosemide. A tracheal aspirate was obtained and was positive for *Pseudomonas aeruginosa*, and she was initiated on IV ceftazidime 50 mg/kg/dose IV every 8 hour on HD 11. However, this was discontinued on HD 12 because she was afebrile and her CRP was within reference range. On HD 17, her SCr and BUN returned to baseline.

She was extubated on HD 22 to high-flow nasal cannula. However, on HD 25, she developed hypercapnic respiratory failure and was intubated and placed on mechanical ventilation. At that time, her CRP was 103.7 mg/L. A tracheal aspirate was performed and was positive for methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, multidrug-resistant *Escherichia coli*, and *Klebsiella pneumoniae*. She was initiated on clindamycin 13 mg/kg/dose IV every 8 hours and piperacillin/tazobactam 100 mg/kg/dose IV every 8 hours from HD 27 to 31. However, she had no elevation in her SCr or other evidence of AKI. She was initiated on nebulized tobramycin 300 mg every 12 hours from HD 32 to 39. On HD 34, she had a tracheostomy performed and was transitioned to a long-term ventilator. On HD 45, she was discharged to the LTC facility on mechanical ventilation via her tracheostomy.

DISCUSSION

Drug-induced AKI is a significant concern in critically ill children. This is one of the first reports of AKI with concomitant piperacillin/tazobactam and vancomycin in a pediatric patient. Vancomycin and piperacillin/tazobactam both independently have the potential to cause AKI through an intrinsic injury to the kidney: vancomycin reportedly through acute tubular necrosis, and penicillin via development of acute interstitial nephritis.[10]

Several recent studies in adults have evaluated the incidence of AKI with vancomycin monotherapy versus combination therapy with vancomycin and piperacillin/tazobactam, but there are few reports in children. Meany et al[1] performed a retrospective-cohort study of 125

Table 3. Clinical Parameters Related to Renal Function

HD	SCr (mg/dL)	BUN (mg/dL)	eGFR (mL/min/1.73m²)	Weight (kg)	UOP (mL/kg/hr)	Fluid Balance (L)	Fluid Overload* (%)	Vancomycin Trough Concentration, (mg/L)
1	0.31	7	216.5	29.9	†	+ 0.8	2.5	
2	0.37	5	181.4	29.9	1.9	+ 1.6	5.2	<5
3	0.44	6	152.5	30.8	4.0	+ 3.2	10.6	17
4	1.16	8	57.8	31	2.8	+ 4.9	16.3	37
5	0.89	8	75.4	33	1.5	+ 5.5	18.3	5
6	0.63	9	106.5	33.2	2.0	+ 4.4	14.8	
7	0.64	15	104.8	33	3.8	+ 3.5	11.6	
8	0.62	36	108.2	34	3.6	+ 1.9	6.4	
9	0.54	36	124.3	33	3.6	+ 1.9	6.3	
10	0.49	33	136.9	32	2.6	+ 1.7	5.8	

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate using Modified Swartz equation[8]; HD, hospital day; SCr, serum creatinine; UOP, urine output

* % Fluid Overload[15] = [Fluid intake (L) – Fluid output (L)]/PICU admission weight (kg)

† Patient transferred from an outside facility to the institution, so UOP was unable to be estimated

adult patients in internal medicine receiving vancomycin. When controlling for potential confounders, they found that patients receiving concomitant piperacillin/tazobactam had an increased risk of developing AKI compared with those on vancomycin monotherapy, with an adjusted odds ratio (OR) of 5.36 (95% confidence interval [CI], 1.41 to 20.5). Three studies have retrospectively compared the incidence of AKI in 1066 adults receiving vancomycin with or without piperacillin/tazobactam.[2–4] Although it is difficult to compare these 3 studies because they used different definitions of AKI, all 3 studies noted that combination therapy was significantly associated with the development of AKI.

An additional 3 studies compared the development of AKI with vancomycin and piperacillin/tazobactam versus vancomycin plus other combinations of antibiotics with conflicting results.[5–7] Two studies that compared the combination of vancomycin and piperacillin/tazobactam versus vancomycin plus other β-lactam antibiotics found no significant difference between groups. These data are difficult to assess because both studies were inadequately powered to detect statistical differences.[5,6] In contrast, Gomes and colleagues[7] found different results. They conducted a matched-cohort study of 112 patients receiving cefepime and vancomycin versus 112 patients receiving piperacillin/tazobactam and vancomycin.[7] They noted a statistically significant difference in the percentage of patients developing AKI in the piperacillin/tazobactam versus the cefepime group (34.8% versus 12.5%; $p < 0.0001$). In addition, they conducted a logistic regression and found that the combination of piperacillin/tazobactam and vancomycin was an independent predictor of AKI ($p = 0.003$). This suggests that the combination of piperacillin/tazobactam and vancomycin may be more likely to induce the development of AKI than other β-lactam combinations.

To date, only one report, to our knowledge, has evaluated the development of AKI with piperacillin/tazobactam in children. Pratt and colleagues[11] present a case series of 4 pediatric patients in oncology who developed AKI during therapy with piperacillin/tazobactam. Three of them were concomitantly receiving vancomycin at the time the AKI developed. All 4 developed AKI within 2 to 3 days of treatment initiation. The authors attributed nephrotoxicity to acute interstitial nephritis secondary to piperacillin/tazobactam, but they hypothesized that the 3

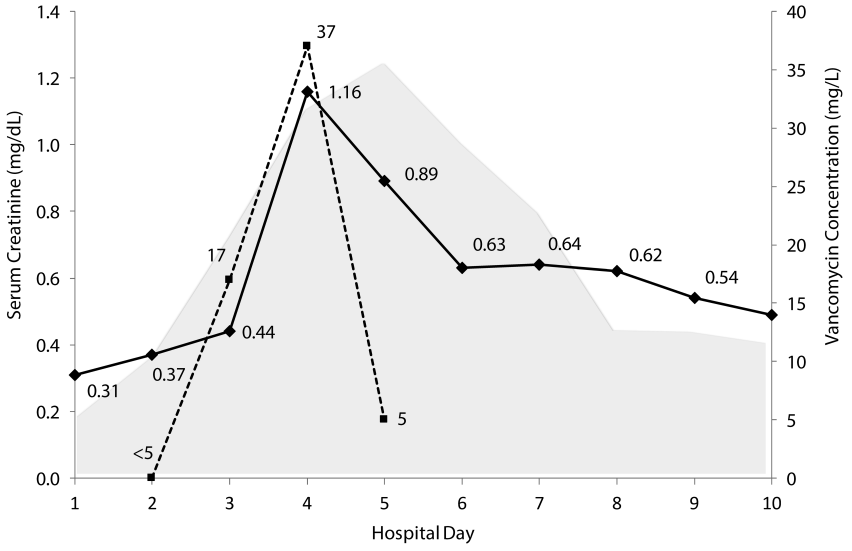

Figure. Changes in serum creatinine, vancomycin concentration, and fluid balance during hospital days 1 to 10.
—— serum creatinine; - - - - vancomycin concentration; □ fluid balance in liters

children receiving vancomycin may have had more-pronounced renal failure because of this combination. It is not clear from these reports what vancomycin concentrations were targeted in these patients. Recent recommendations from the Infectious Disease Society of America have suggested targeting vancomycin concentrations at 15 to 20 mg/L in adults and children for serious infections including pneumonia.[12] Our patient's vancomycin dose was increased to achieve a trough concentration within that range given the severity of her infection. It is feasible that the increased dose of vancomycin may have increased the likelihood of AKI. However, a recent study by Cies and colleagues[13] has suggested that maintaining vancomycin concentrations at 15 to 20 mg/L was not associated with the development of AKI. Therefore, it seems likely that the combination therapy may be associated with a greater risk of AKI in children than vancomycin monotherapy alone.

Our patient's clinical course was complicated by development of fluid overload and ARDS. Recently, fluid overload has been associated with negative outcomes in critically ill children.[14,15] Arikan and colleagues[14] retrospectively evaluated the association between fluid overload and oxygenation in 80 children. They found that fluid overload ≥15% was independently associated with the daily oxygenation index when controlling for age, gender, and Pediatric Logistic Organ Dysfunction ($p < 0.05$). Additionally, they noted that peak fluid overload was independently associated with longer ventilator duration ($p = 0.004$) and PICU length of stay ($p = 0.008$). Another recent study[15] found that a cumulative positive fluid balance in children with significant shock was associated with PICU mortality.

Our patient's peak fluid overload was 18.3% on HD 5. It is reasonable to assume that this increase in fluid balance may have led to her worsening respiratory status. Because it is not clear what role the positive fluid balance had in increasing the potential for AKI in our patient, we used the Naranjo adverse drug reaction probability scale to assess the likelihood that AKI occurred because of vancomycin and piperacillin/tazobactam. The Naranjo scale is a validated tool commonly used to assess potential drug-related adverse events.[16] When applied to our patient's case, a score of 5 was calculated, indicating a probable drug-related adverse event for the combination of piperacillin/tazobactam and vancomycin. Notably, after resolution of AKI, our patient was restarted on piperacillin/tazobactam on HD 27 to 31 and did not develop signs of recurrent AKI.

Given the lack of data, it is difficult to determine the true incidence of AKI with piperacillin/tazobactam and vancomycin in children. Providers should be aware of the potential additive nephrotoxicity that this combination may have. Clinicians should follow strict assessment of the patient's fluid balance, follow UOP closely, and assess SCr every 1 to 2 days of concomitant therapy. It is the authors' opinion that children receiving doses of vancomycin ≥60 mg/kg/day should have trough concentrations assessed every 3 to 5 days, at a minimum. In children who meet the criteria for AKI based on the pediatric-modified RIFLE criteria, vancomycin concen-

trations should be assessed as soon as possible, and clinicians should consider discontinuation of piperacillin/tazobactam and vancomycin in favor of other suitable alternatives.

CONCLUSION

In conclusion, we describe a patient who developed AKI during concomitant vancomycin and piperacillin/tazobactam, which resolved after both drugs were discontinued and did not recur with recommencement of piperacillin/tazobactam monotherapy. Despite the patient's clinical course being complicated by cumulative fluid overload and ARDS, clinicians must be aware of the possibility of AKI with this antibiotic combination. Vigilant monitoring of renal function and vancomycin concentrations is indicated. Future prospective studies are needed to explore the incidence and clinical characteristics associated with AKI and this drug combination in children.

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Abbrevations AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BiPAP, bilevel positive airway pressure; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; HD, hospital day; IV, intravenous; LTC, long-term care; SCr, serum creatinine; PICU, pediatric intensive care unit; RIFLE, risk, injury, failure, loss, end-stage disease; UOP, urine output; WBC, white blood cell

Correspondence Peter N. Johnson, PharmD, BCPS, BCPPS, FPPAG, University of Oklahoma, College of Pharmacy, 1110 N Stonewall Ave, CPB 206, Oklahoma City, OK 73117, email: peter-johnson@ouhsc.edu

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