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Incidence and Risk Factors for Vancomycin Nephrotoxicity in Acutely Ill Pediatric Patients

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Abstract

Background: Particularly with the current increased vancomycin dosing trends, the true risk of the agent's nephrotoxicity is not well characterized and remains of concern. **Objective:** To determine the incidence of vancomycin nephrotoxicity in acutely ill hospitalized children and to secondarily characterize the risk factors for this complication. **Methods:** A single-center retrospective cohort study conducted at UCSF Benioff Children's Hospital from June 2012 to June 2015. Inpatients 3 months to <19 years who received intravenous vancomycin for ≥48 hours were included. The primary outcome was incidence of nephrotoxicity, defined as an increase in serum creatinine by ≥50% from baseline. Univariate and multivariate analyses were conducted to identify risk factors for vancomycin nephrotoxicity. **Results:** A total of 291 patients (272 nonnephrotoxic and 19 nephrotoxic) were included in the analysis. Of the 19 patients, 12 (4.1%) were found to have moderate to severe toxicity. The median duration of therapy was 3 (3-5) and 4 (3-6) days for the group with "no nephrotoxicity" and "nephrotoxicity," respectively. The mean time for the serum creatinine to return to normal in patients with nephrotoxicity was 5.1 days. In the multivariate analysis, only final trough concentration ≥15mg/dL (odds ratio = 3.49, 95% confidence interval = 1.2-10.1; $P = .021$) and receipt of piperacillin/tazobactam (odds ratio = 3.14, 95% confidence interval = 1.02-9.6; $P = .046$) were significantly associated with nephrotoxicity. **Conclusion:** The rate of moderate to severe vancomycin-associated nephrotoxicity in acutely ill children is relatively uncommon and reversible. Kidney injury is associated with increased vancomycin trough concentrations and concomitant receipt of nephrotoxins, particularly piperacillin/tazobactam.

Keywords

vancomycin, pediatrics, nephrotoxicity, therapeutic drug monitoring, antibiotics

Background

Vancomycin is a bactericidal, glycopeptide antibiotic widely used for the treatment of infection due to methicillin-resistant *Staphylococcus aureus*.[1,2] The original formulations of intravenous vancomycin contained impurities that were associated with nephrotoxicity and ototoxicity, which limited its use. However, the current formulations have virtually eliminated these impurities.[3] Particularly with the current increased vancomycin dosing trends, the true risk of the agent's nephrotoxicity is not well characterized and remains of concern.[3-5]

In 2009, a consensus statement regarding the use of vancomycin in adults was published by the American Society of Health-System Pharmacists (ASHP), the Infectious Disease Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP).[5] The guidelines recommended increased vancomycin troughs of 15 to 20 mg/L, as compared with the traditional troughs of 5 to 15 mg/L, for complicated *Staphylococcus aureus* infections. Similarly, the American Thoracic Society published guidelines recommending a serum trough of 15 to 20 mg/L for hospital-acquired, ventilator-associated, and health care–associated pneumonia.[6] While guidelines exist for adults, similar recommendations do not exist for pediatric patients. Despite the absence of guidelines, more aggressive vancomycin dosing regimens have been used in children. As with adults, a concern exists that more aggressive dosing could increase the risk for vancomycin nephrotoxicity in children.

The ASHP/IDSA/SIDP recommendations for adults have resulted in adjustment of guidelines with more aggressive vancomycin dosing in many pediatric hospitals.[5] While several investigators have evaluated the necessary dosage

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to achieve serum vancomycin trough concentrations of 15 to 20 mg/L in children, it is not clear whether these increased doses and associated levels are associated with an increased risk of nephrotoxicity.[7-12] In addition, vancomycin pharmacokinetics and pharmacodynamics between children and adults differ; consequently, results from adult studies may not reflect that observed in children.[8]

Retrospectively performed studies in adults have demonstrated that increased vancomycin dosage and increased serum vancomycin trough concentrations (≥15 mg/L) are associated with an increased risk for nephrotoxicity.[13-18] Studies in children suggest that renal function, duration of therapy, vancomycin serum trough concentration ≥15 mg/L, intensive care unit admission, and concurrent administration of nephrotoxic medications increase the risk for nephrotoxicity.[1,4,19-23] In contrast, a study of pediatric intensive care unit patients revealed that vancomycin trough concentrations ≥15 mg/L were not associated with an increased rate of nephrotoxicity.[3] Therefore, the incident, severity, and associated risk factors remain unclear and continue to be debated.

Our goal was to determine the incidence of vancomycin nephrotoxicity in pediatric patients at a tertiary care center. Secondarily, the goal was to identify the risk factors associated with this complication.

Methods

The University of California San Francisco institutional review board approved the study. A single-center retrospective cohort study was conducted at UCSF Benioff Children's Hospital, a tertiary care teaching hospital. Patients admitted from June 1, 2012, to June 30, 2015, and aged 3 months through 18 years who received vancomycin for ≥48 hours were included. Included patients required blood urea nitrogen (BUN) and serum creatinine (SCr) data 72 hours pre and post vancomycin administration and serum vancomycin trough levels. Patient enrolled outside this time period, with less than 3 months of age, insufficient length of therapy, or without BUN, SCr 72 hour pre and post vancomycin therapy were excluded. Depending on the patient's clinical status and location in the pediatric hospital (primarily intensive care unit vs general ward), the frequency of SCr measurement took place at least daily, ranging from every 2 to 24 hours. Of note, all patients who receive vancomycin at Benioff Children's Hospital receive therapeutic drug monitoring from pediatric pharmacists.

Data collected from patient medical records included patient demographics, vancomycin dosage and serum levels, and potential risk factors for renal failure including concomitant nephrotoxic medications. Study data were collected and managed using REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at UCSF.[24] Patient characteristics included gender, age, weight, initial and final BUN and SCr. Vancomycin-specific information included vancomycin dosage, duration of therapy, and initial and final trough concentration. The hospital clinical chemistry laboratory used the IDMS traceable enzymatic assay on Beckman DXC 600/800 analyzers for SCr and the turbidimetric inhibition immunoassay (Beckman DxC800) for determining the serum vancomycin concentrations during the study period. Potential risk factors in our model included hypotension, respiratory dysfunction, and preexisting renal dysfunction. Hypotension was defined as documented history of hemodynamic instability requiring vasoactive medications, septic shock, and multi-organ failure. Respiratory dysfunction was defined as documented acute respiratory distress syndrome, acute respiratory failure, need for extracorporeal membrane oxygenation, and respiratory support requiring mechanical ventilation. Preexisting renal dysfunction was defined as documented history of renal dysfunction and/or renal transplant. Common concomitant nephrotoxic medications included intravenous (IV) acyclovir, IV amphotericin B liposome, cyclosporine (IV), furosemide (IV, oral), ibuprofen (oral), meropenem (IV), methotrexate (IV), piperacillin/tazobactam (IV), tacrolimus (IV, oral), and tobramycin (IV). Concomitant nephrotoxic medications were dichotomized as yes/no if received at any time during the treatment course and did not need to be administered for the entire duration of vancomycin therapy.

In those patients receiving multiple courses of therapy, only the initial course was evaluated. Nephrotoxicity was defined as an increase in SCr by ≥50% from baseline, as adopted from the Pediatric-Modified RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria (pRIFLE).[25] Baseline SCr was defined as SCr sampled ≤72 hours prior to initiating vancomycin therapy. Nephrotoxicity was further categorized as "mild" and "moderate to severe" nephrotoxicity. The normal range for SCr in the pediatric hospital is 0.3 to 0.9 mg/dL. Those patients whose final SCr increased to >0.9 mg/dL were considered to have "moderate to severe" nephrotoxicity, while those whose SCr increased by ≥50% from baseline but did not exceed this threshold were considered to experience "mild" disease. Serum vancomycin trough concentrations >10 mg/L were recommended for empirical or definitive *S aureus* infections. Trough concentrations of 15 to 20 mg/L were recommended for complicated infections, which included bacteremia, endocarditis, osteomyelitis, meningitis, and pneumonia. Severe infections, including bacteremia, were treated with vancomycin 15 to 20 mg/kg/dose IV q6-8h (initial maximum 1 g/dose).

A random sampling of 10% of the total vancomycin treatment courses took place to confirm the quality associated with the data collection. A total of 42 vancomycin treatment courses (42 different patients) were randomly selected and evaluated for documentation errors. No errors were observed, and the final data were submitted for statistical analysis.

Statistical Analysis

Continuous characteristics of patients are presented using measures of the central tendency, mean of normally distributed data, or median for skewed data as assessed using Shapiro-Wilks test, and variability was estimated using variance or interquartile range accordingly. Baseline demographic and clinical characteristics between nephrotoxicity and nonnephrotoxicity patients were compared using Mann-Whitney test and χ^2 test. A 2-sided significance level of an α of .05 was used to determine statistical significance. Both univariate and multivariate analysis were performed to identify variables associated with development of nephrotoxicity. Covariates included gender, age, weight, initial and final BUN and SCr, initial and final vancomycin dose, duration of therapy, initial and final serum vancomycin trough concentration, and concomitant nephrotoxic risk factors including medications. Statistically significant factors ($P < .05$) identified from the univariate analysis were analyzed using a multivariable logistic model. Odds ratios (ORs) were computed in the final model for all included variables. All analysis was performed using SAS 9.4 (Cary, North Carolina).

Results

A total of 1029 patients received vancomycin therapy during the study period. Of these patients, 738 were excluded primarily due to insufficient duration of therapy or not satisfying the selected age range. Eight patients' records were unavailable. A total of 291 patients receiving 415 courses of vancomycin therapy were ultimately included for analysis. Of the 291, 66 patients received multiple courses (n = 190). Of the 291 patients, 19 (6.5%) met our definition for nephrotoxicity.

Patient demographics and clinical characteristics are shown in Table 1. Gender, age, and initial BUN and SCr did not differ between those with and without nephrotoxicity. However, hypotension, respiratory dysfunction, final trough ≥15 mg/L, and concomitant use of other nephrotoxins were significantly more likely observed in the nephrotoxicity group. In addition, median weight, median initial and final dose, and median final BUN and SCr were significantly greater in those patients who experienced nephrotoxicity.

Nephrotoxicity was further divided into "mild" and "moderate to severe" nephrotoxicity (Table 2). Twelve out of 291 (4.1%) patients met our definition of moderate to severe nephrotoxicity. Moderate to severe nephrotoxicity patients were treated in the pediatric critical care (n = 5), pediatric bone marrow transplant (BMT; n = 2), pediatric hematology/oncology (n = 3), pediatric hospital medicine (n = 1), and orthopedics (n = 1), respectively. In the "mild" nephrotoxicity group, patients were housed in the pediatric hematology/oncology (n = 1), pediatric BMT (n = 1), pediatric critical care (n = 4), and pediatric hospital medicine (n = 1) units, respectively. Age, weight, initial and final dose, hypotension, respiratory dysfunction, final serum vancomycin trough concentration ≥15 mg/L, and receipt of concomitant medications (acyclovir, amphotericin B liposome, methotrexate, piperacillin/tazobactam, and tobramycin) were significantly more likely to be associated with moderate to severe nephrotoxicity. In contrast, an initial serum vancomycin trough ≥15 mg/L and receipt of meropenem were more likely observed in those patients with mild toxicity.

All patients who fulfilled our definition for toxicity had at least one concomitant risk factor for nephrotoxicity. All patients (n = 19) with toxicity received at least one concomitant nephrotoxic medication. Of these patients, 14/19 (74%) were found to have ≥2 concomitant risk factors, and 9/19 (47%) had ≥3 risk factors. Patients with moderate to severe toxicity had an average of 2.8 concomitant risk factors, while those with mild toxicity had 1.9. In those patients with moderate to severe disease, SCr returned to normal in all but one patient. The mean time for the SCr to return to normal in these patients was 5.1 days. When compared with patients with vancomycin trough levels <15 mg/L, those with final troughs ≥15 mg/L took longer for the SCr to return to normal when compared with those with final troughs <15 mg/L (6.1 vs 2 days). Among those patients with toxicity and associated trough levels ≥15 mg/L, one died while receiving vancomycin therapy; the death was not attributed to vancomycin. Patients in the mild nephrotoxicity group who did not experience a SCr rise above the medical center normal upper limit were included in this latter analysis.

In an effort to confirm whether the increased vancomycin troughs were associated with subsequent increase in creatinine versus the increase in serum creatinine resulting in accumulation of vancomycin and associated troughs, we provided an additional review of those patients with moderate to severe nephrotoxicity. Of these patients, 75% (9/12) had final serum vancomycin trough concentration ≥15 mg/L. Of these 9 patients, 6 had trough >20 mg/dL. Furthermore, 66.7% (6/9) of patients with final trough ≥15 mg/L unequivocally experienced acute kidney injury (AKI) after final serum vancomycin trough collection. In the other 3 patients, it was not possible to determine whether the rise in serum creatinine preceded or followed the vancomycin trough. All 3 patients with final trough <15 mg/L experienced AKI after the final serum vancomycin trough collection.

All factors found to be significant in the univariate model were included in the final multivariate model. These factors included weight, initial and final vancomycin dose, final serum vancomycin trough concentration ≥15 mg/L, hypotension, respiratory dysfunction, receipt of concurrent nephrotoxins including intravenous acyclovir, amphotericin B liposome, furosemide, methotrexate, piperacillin/tazobactam, and tobramycin. The multivariate analysis revealed

Table 1. Characteristics of Pediatric Patients With and Without Nephrotoxicity.

	All Patients (n = 291)	No Nephrotoxicity (n = 272)	Nephrotoxicity (n = 19)	*P*
Patient characteristics				
Male, n (%)	179 (61.5%)	162 (55.7%)	11 (57.9%)	.89[a]
Age (years)[b]	6.6 ± 5.7	6.5 ± 5.72	8.8 ± 5.09	.055[c]
Weight (kg)[d]	17.8 (8.9-38.8)	17.4 (8.6-37.9)	27.4 (21.6-49.9)	.037[c]
Initial BUN (mg/dL)[d]	9 (6-14)	9 (6-14)	9 (5-15)	.99[c]
Final BUN (mg/dL)[d]	9 (5-13)	8 (5-13)	17 (11-34)	.0001[c]
Initial SCr (mg/dL)[d]	0.34 (0.3-0.5)	0.34 (0.3-0.5)	0.38 (0.3-0.52)	.50[c]
Final SCr (mg/dL)[d]	0.31 (0.3-0.5)	0.3 (0.3-0.455)	1.01 (0.79-1.19)	<.0001[c]
Vancomycin information				
Initial dose (mg/dose)[d]	300 (144-600)	287 (139-580)	500 (345-750)	.021[c]
Initial dose (mg/kg/dose)	16.8	16.5	18.2	
Final dose (mg/dose)[d]	343 (189-650)	325 (184-615)	540 (400-800)	.013[c]
Final dose (mg/kg/dose)	19.2	18.7	19.7	
Duration of therapy (days)[d]	3 (3-5)	3 (3-5)	4 (3-6)	.096[c]
Initial trough ≥15 mg/L, n (%)	43 (14.8%)	38 (14.0%)	5(26.3%)	.14[a]
Initial trough range (mg/L)	1-27	1-27	3-27	
Initial trough time after initial dose (hours)[e]	21.9 (7-126)	21.7 (7-126)	23.8 (12-47)	
Final trough ≥15 mg/L	68 (23.4%)	57 (21.0%)	11 (57.9%)	.0002[a]
Final trough range (mg/L)	3-60	3-28	9-60	
Final trough to final dose (hours)[e]	19.8 (0-120)	20 (0-120)	16 (0-96)	
Nephrotoxic factors, n (%)				
Hypotension	29 (10%)	23 (8.5%)	6 (31.65%)	.0011[a]
Respiratory dysfunction	76 (26.1%)	67 (24.6%)	9 (47.4%)	.029[a]
Preexisting renal dysfunction	12 (4.1%)	10 (3.7%)	2 (10.5%)	.15[a]
Nephrotoxic medications, n (%)				
Acyclovir (IV)	31 (10.7%)	26 (9.6%)	5 (26.3%)	.022[a]
Amphotericin B liposome (IV)	12 (4.1%)	9 (3.3%)	3 (15.8%)	.0082[a]
Cyclosporine (IV)	14 (4.8%)	12 (4.4%)	2 (10.5%)	.23[a]
Furosemide (IV/PO)	106 (36.4%)	95 (34.9%)	11 (57.9%)	.044[a]
Ibuprofen (PO)	34 (11.7%)	32 (11.8%)	2 (10.55%)	.87[a]
Meropenem (IV)	44 (15.1%)	39 (14.3%)	5 (26.3%)	.16[a]
Methotrexate (IV)	7 (2.4%)	5 (1.8%)	2 (10.5%)	.017[a]
Piperacillin/tazobactam (IV)	123 (42%)	110 (40.4%)	13 (68.4%)	.017[a]
Tacrolimus (IV/PO)	23 (7.9%)	21 (7.7%)	2 (10.5%)	.66[a]
Tobramycin (IV)	28 (9.6%)	23 (8.5%)	5 (26.3%)	.011[a]

Abbreviations: BUN, blood urea nitrogen; IV, intravenous; PO, oral; SCr, serum creatinine; SD, standard deviation.
[a]Based on χ^2 test.
[b]Mean ± SD.
[c]Based on Mann-Whitney test.
[d]Median (Q1-Q3).
[e]Average.

that only a serum vancomycin trough ≥15 mg/L and concomitant receipt of piperacillin/tazobactam were independently associated with nephrotoxicity (Table 3).

Discussion

Following its approval in the 1950s, vancomycin has been associated with nephrotoxicity, most likely due to the lack of purity of the product. Since that time, vancomycin has been manufactured without the impurities associated with the older product. Despite the reformulation of the product, debate remains whether the currently used vancomycin independently causes nephrotoxicity. Furthermore, due to an increased vancomycin dosing strategies, we have seen resurgence in nephrotoxicity with unclear mechanism.

The 2009 ASHP/IDSA/SIDP recommendations regarding vancomycin resulted in more aggressive dosing not only in adults, but also in children. In adults, increasing the dose of vancomycin can optimize the pharmacodynamics outcome (AUC/MIC ratio).[5] However, the AUC/MIC ratio is

Table 2. Comparing Patients Without Nephrotoxicity With Mild Nephrotoxicity and Moderate to Severe Nephrotoxicity.

	No Nephrotoxicity (n = 272)	Moderate to Severe Nephrotoxicity (n = 12)	*P*	Mild Nephrotoxicity (n = 7)	*P*
Patient characteristics					
Male, n (%)	162 (55.7%)	7 (58.3%)	.93[a]	4 (57.1%)	.9[a]
Age (years)[b]	6.45 ± 5.72	10.6 ± 4.68	.014[c]	5.53 ± 4.28	.98[c]
Weight (kg)[d]	17.4 (8.6-37.9)	43.9 (23.5-53.4)	.014[c]	23 (14.3-28)	.79[c]
Initial BUN (mg/dL)[d]	9 (6-14)	12 (7-14)	.61[c]	8 (5-27)	.52[c]
Final BUN (mg/dL)[d]	8 (5-13)	17 (12.5-29)	.0015[c]	14 (8-36)	.024[c]
Initial SCr (mg/dL)[d]	0.34 (0.3-0.5)	0.47 (0.34-0.55)	.12[c]	0.33 (0.3-0.38)	.36[c]
Final SCr (mg/dL)[d]	0.3 (0.3-0.455)	1.09 (1.03-1.45)	<.0001[c]	0.61 (0.55-0.8)	<.0001[c]
Vancomycin information					
Initial dose (mg/dose)[d]	287 (139-580)	643 (386-890)	.0096[c]	420 (231-500)	.65[c]
Initial dose (mg/kg/dose)	16.5	14.6		18.2	
Final dose (mg/dose)[d]	325 (184-615)	690 (500-975)	.0083[c]	500 (308-700)	.48[c]
Final dose (mg/kg/dose)	18.6	15.7		21.7	
Duration of therapy (days)[d]	3 (3-5)	4.5 (3-6.5)	.15[c]	4 (3-6)	.36[c]
Initial trough ≥15 mg/L, n (%)	38 (14.0%)	2 (16.7%)	.79[a]	3 (42.9%)	.033[a]
Initial trough range (mg/L)	1-27	3-27		5-19	
Initial trough time after initial dose (hours)[e]	21.7 (7-126)	26 (12-47)		20 (12-36)	
Final trough ≥15 mg/L	57 (21.0%)	9 (75%)	<.0001[a]	2 (28.6%)	.63[a]
Final trough range (mg/L)	3-28	12-60		9-18	
Final trough to final dose (hours)[e]	20 (0-120)	9.4 (0-30)		31.1(0-96)	
Nephrotoxic factors, n (%)					
Hypotension	23 (8.5%)	6 (50%)	.0001[a]	0 (0.0%)	.42[a]
Respiratory dysfunction	67 (24.6%)	6 (50%)	.049[a]	3 (42.9%)	.27[a]
Preexisting renal dysfunction	10 (3.7%)	1 (8.3%)	.41[a]	1 (14.3%)	.15[a]
Nephrotoxic medications					
Acyclovir (IV)	26 (9.6%)	5 (41.7%)	.0005[a]	0 (0.0%)	.39[a]
Amphotericin B liposome (IV)	9 (3.3%)	2 (16.7%)	.019[a]	1 (14.3%)	.12[a]
Cyclosporine (IV)	12 (4.4%)	2 (16.7%)	.055[a]	0 (0.0%)	.57[a]
Furosemide (IV/PO)	95 (34.9%)	7 (58.3%)	.098[4]	4 (57.1%)	.23[a]
Ibuprofen (PO)	32 (11.8%)	1 (8.3%)	.72[a]	1 (14.3%)	0.84[a]
Meropenem (IV)	39 (14.3%)	2 (16.7%)	.82[a]	3 (42.9%)	.037[a]
Methotrexate (IV)	5 (1.8%)	2 (16.7%)	.0012[a]	0 (0.0%)	.72[a]
Piperacillin/tazobactam (IV)	110 (40.4%)	10 (83%)	.0032[a]	3 (42.9%)	.90[a]
Tacrolimus (IV/PO)	21 (7.7%)	2 (16.7%)	.27[a]	0 (0.0%)	.44[a]
Tobramycin (IV)	23 (8.5%)	4 (33.3%)	.0040[a]	1 (14.3%)	.59[a]

Abbreviations: BUN, blood urea nitrogen; IV, intravenous; PO, oral; SCr, serum creatinine; SD, standard deviation.
[a]Based on χ^2 test.
[b]Mean ± SD.
[c]Based on Mann-Whitney test.
[d]Median (Q1-Q3).
[e]Average.

not easily calculated nor easily utilized in clinical practice. Consequently, the surrogate marker, serum trough concentrations, is often used as a predictor of optimal AUC/MIC ratio and associated vancomycin efficacy and toxicity.[5] Previous studies in children have suggested that vancomycin trough concentrations of 7 to 10 mg/L are correlated with the optimal AUC/MIC ratio of 400. These studies also question whether targeting increased trough concentrations increase the risk for vancomycin associated nephrotoxicity.[9,10]

In adults, the rate of vancomycin-associated nephrotoxicity ranges from 13% to 43%.[13,14] However, nephrotoxicity data in children are more limited with a reported rate ranging from 8.8% to 19%.[3,4,19-21,23] Our study results differ those previously reported. First, both the incidence and severity of vancomycin-associated toxicity in our study were less than that previously observed. We documented only a 6.5% (19 of 291) incidence of vancomycin nephrotoxicity in high-risk children as defined by pRIFLE.[25] If

Table 3. Multivariate Logistic Models for the Occurrence of Nephrotoxicity.

Variable	OR	95% CI	*P*
Final trough ≥15 mg/L	3.49	1.2-10.1	.021
Piperacillin/tazobactam (IV)	3.14	1.02-9.6	.046
Weight	1	0.98-1.03	.38
Hypotension	2.9	0.82-9.9	.99
Respiratory dysfunction	1.9	0.59-6.1	.28
Acyclovir (IV)	1.6	0.45-6.5	.48
Furosemide (IV/PO)	1.9	0.57-6	.3
Tobramycin (IV)	2.7	0.66-11.1	.17

Abbreviations: OR, odds ratio; CI, confidence interval; IV, intravenous; PO, oral.

only those children whose SCr ultimately exceeded the upper normal limit are included in the analysis, only 12/291 (4.1%) of our patients experienced what we would characterize as clinically significant toxicity. Of the 12 patients exceeding the upper limit, using KDIGO definitions of acute renal failure,[26] 3 would be considered Stage 1 (SCr increased to 1.5-1.9 times baseline), 7 would be classified as Stage 2 (SCr increased to 2-2.9 times baseline), and 2 patients would have experienced Stage 3 (SCr increased to 3 times baseline). In the 2 patients experiencing Stage 3 toxicity, neither required dialysis and both had SCr return to baseline.

Our study also differs from others regarding risk factors for toxicity. Previous studies in children identified receipt of nephrotoxins[21] and elevated vancomycin trough levels[4,14,20] as risk factors for renal failure. Our univariate analysis revealed concomitant use of nephrotoxic medications to be present more commonly in patients with nephrotoxicity. All concomitant nephrotoxic medications were confirmed to have been administered during the course of vancomycin therapy. The duration of therapy for each concomitant nephrotoxin was not collated. Of note, every patient who developed AKI concomitantly received one or more of the studied nephrotoxins. Also noteworthy in our study was the significant association with concomitant use of piperacillin/tazobactam. Of note, piperacillin/tazobactam was not highly statistically significant. In an effort to confirm whether receipt of piperacillin/tazobactam preceded nephrotoxicity, we further investigated patients with nephrotoxicity (n = 19) and found receipt of piperacillin/tazobactam preceded nephrotoxicity in all (n = 13) patients who received this agent during the course of vancomycin therapy. Similar results have been reported recently in adults.[27,28]

While the final vancomycin concentration was significantly associated with nephrotoxicity, the same association was not observed with the initial serum level. Our multivariate analysis identified final serum vancomycin trough concentration ≥15 mg/L to be an independent factor associated with nephrotoxicity; these results are consistent with that of others.[18] Though vancomycin serum trough concentration ≥15 mg/L have been associated with nephrotoxicity in pediatric studies, the retrospective method of our analysis makes it difficult to unequivocally link the cause and effect relationship between trough concentrations and AKI retrospectively, a similar challenge for previously published investigations.[4] As others have stated, a reduction in kidney function from any cause would lead to increased vancomycin troughs and would not necessarily indicate vancomycin induced AKI.[4,29]

Duration of therapy has been reported to increase the risk for nephrotoxicity in both adults and pediatric patients treated with vancomycin.[3,4,13] In our study, the median duration of therapy was 4 days in the nephrotoxicity group and 3 days in those without toxicity; however, this difference was not found to be significant. It may well be that the shorter duration of vancomycin therapy contributed to the inability to link duration with toxicity. Nonetheless, these durations represent the real world use of this agent in a tertiary academic pediatric hospital.

In addition to its retrospective design, there were several limitations to our study. Our definition of nephrotoxicity using pRIFLE depended on SCr, which could have limited our ability to identify nephrotoxicity. Transient variations including acceptable laboratory error could have incorrectly placed a child in the nephrotoxicity cohort. We also acknowledge that our definition of "mild" and "moderate to severe" toxicity are not validated; however, this categorization provides the clinician with a sense for whether the elevation in creatinine was clinically significant. It is also possible that the normalization of serum creatinine may not be reflective of more long-term toxicity associated with acute nephrotoxin exposure.[30] However, it is encouraging that all but one of these patients ultimately had their serum creatinine return within the normal range. The results may have been affected by the fact that the frequency of serum creatinine sampling varied widely among patients; not surprisingly, patients in the intensive care unit setting had more frequent sampling compared with that observed on the general wards. Although many nephrotoxins were evaluated, other important medications may not have been considered. As stated previously, it is also possible that elevated vancomycin troughs were a result of a decline in renal function rather than vancomycin-causing kidney injury. Last, the median vancomycin duration of therapy was <5 days, potentially limiting the evaluation of duration as a risk factor.

Conclusion

Clinically significant nephrotoxicity is uncommon in acutely ill pediatric patients. When vancomycin nephrotoxicity does occur, it is reversible, even in acutely ill patients. Finally, our

experience suggests that if vancomycin is nephrotoxic, it most commonly occurs with the concomitant use of known nephrotoxins, particularly piperacillin/tazobactam.

Authors' Note

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