Vancomycin-Associated Nephrotoxicity and Risk Factors in Critically Ill Children Without Preexisting Renal Injury

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Background: A recent systematic review concluded that critically ill pediatric patients have higher odds of vancomycin-related nephrotoxicity [odds ratio (OR): 3.61, 95% CI: 1.21–10.74]. We aimed to assess the incidence and risk factors for vancomycin-associated nephrotoxicity in critically ill children without preexisting renal injury.

Methods: A cohort of children admitted to a pediatric intensive care unit, from 2011 to 2016 treated with vancomycin without preexisting renal injury. The main diagnosis, therapeutic interventions and medications administered in this period were evaluated. Generalized estimating equation models were used to assess the association between clinical covariates and the dependent variable pediatric risk, injury, failure, loss, end-stage renal disease (pRIFLE).

Results: Hundred ten patients, representing 1177 vancomycin days, were analyzed. Vancomycin-associated nephrotoxicity was seen in 11.8%. In a multivariate model, higher vancomycin doses were not associated with poorer renal function (P = 0.08). Higher serum vancomycin levels were weakly associated with pRIFLE classification (OR: 1.05, 95% CI: 1.02–1.07). Furosemide or amphotericin B in addition to the vancomycin treatment was associated with impaired renal function (OR: 2.56, 95% CI: 1.38–4.8 and OR: 7.7 95% CI: 2.55–23, respectively).

Conclusions: Vancomycin-associated nephrotoxicity in acute ill children without preexisting renal injury, measured with pRIFLE, is close to 11.8%. Furosemide and amphotericin B in addition to the vancomycin treatment are strong predictors of worse pRIFLE scores. The influence of acute kidney injury status at pediatric intensive care unit admission and the method used for renal function assessment might influence the incidence of vancomycin-associated nephrotoxicity and its associated risk factors.

Key Words: nephrotoxicity, pediatric, vancomycin, renal injury, critical care

(*Pediatr Infect Dis J XXX;XX:*00–00)

Vancomycin is a glycopeptide antibiotic used for more than 60 years, which covers Gram-positive microorganisms, such as methicillin-resistant *Staphylococcus aureus*.[1] Renal injury is one of the most reported vancomycin-related adverse events, but its mechanism of toxicity still is not fully elucidated.[2]

Several risk factors might contribute to vancomycin-induced nephrotoxicity; however, most of them are inconclusive or even contradictory.[2–4] Few authors suggest that risk factors for vancomycin-induced acute kidney injury (AKI) include vancomycin serum levels greater than 15 mg/L[2–4] and concomitant use of nephrotoxic drugs, such as vasoactive agents and diuretics (eg, furosemide).[5,6] These findings contrast with other studies, in which neither high vancomycin serum levels (P = 0.48)[7–9]nor concomitant use of nephrotoxins drugs were associated with AKI (P = 0.37).[9] That is, the last studies might suggest that prerenal AKI caused by sepsis could, per se, lead to renal dysfunction.[10,11] The last systematic review with meta-analyses about vancomycin-related AKI suggested that trough levels ≥15 mg/L could increase the risk for nephrotoxicity by 2.7-fold [odds ratio (OR): 2.71, 95% CI: 1.82–4.05; I2 = 40%]. This odds were further increased among patients treated in the pediatric intensive care unit (PICU) (OR: 3.61, 95%CI: 1.21–10.74; I2 = 45%).[11]

Few studies did not specify whether patients had AKI by the time vancomycin was started as therapy. Additionally, a different statistical model, rather than logistic regression, might be needed to assess AKI more accurately through time, given that vancomycin serum levels, renal function, and risk factors vary significantly in critically ill children.

The aim of this study was to assess the incidence and risk factors for vancomycin-associated nephrotoxicity in critically ill pediatric patients without preexisting renal injury, by using a generalized estimating equation (GEE) as a statistical model.

METHODS

A retrospective cohort study was conducted in one of the largest general university hospitals in Porto Alegre, Brazil. This study was approved by the local Institutional Review Board and waived the requirement for obtaining informed consent and parental permission.

PICU patients that used vancomycin were initially searched through electronic medical records and pharmacy dispensation registries, from January 1, 2011 to December 31, 2016. Inclusion criteria in the study were defined as: children (<18 years) admitted to the PICU without AKI by the time vancomycin was started as treatment. Additionally, patients should have at least 2 serum creatinine (SCr) values; vancomycin trough levels during treatment; and using nephrotoxic drugs (as described below) throughout the vancomycin treatment course with at least 48 hours of PICU stay. Patients were excluded if they presented with renal injury at baseline PICU admission [as per pediatric risk, injury, failure, loss, end-stage renal disease (pRIFLE) criterion]; or if they started vancomycin for prophylactic purposes. Patients on prophylaxis were excluded because they usually use vancomycin for 1 day and the focus of this article is treatment. When multiple vancomycin cycles were presented, only the first course was considered for this study.

Independent predictors for worse pRIFLE scores included: age, weight, height, pediatric index of mortality II (PIM2), PICU admission diagnosis, comorbidities, serum creatinine, vancomycin dose, administration frequency, serum vancomycin level, treatment duration, concomitant use of nephrotoxins (acyclovir, amphotericin B, amikacin, cyclosporine, ganciclovir, piperacillin/tazobactam, polymyxin B, tacrolimus, and vasoactive drugs), concomitant use

Accepted for publication May 4, 2019.
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The authors have no funding or conflicts of interest to disclose.
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ISSN: 0891-3668/19/XXXX-00
DOI: 10.1097/INF.0000000000002391

of diuretics (furosemide, spironolactone and hydrochlorothiazide), 28-day mortality after vancomycin therapy, and among other covariates.

The primary outcome was pRIFLE scores,[12] which was also used as dependent variable in the GEE model. pRIFLE considers the reduction of estimated creatinine clearance (eCC) by ≥50% from baseline.[3,4,7] eCC was calculated by using the Schwartz equation[13] (0.413 × height/SCr) for patients ≥1 year; for smaller ones, a factor (k) of 0.45 was used. The secondary outcome was AKI risk factors, defined by the aforementioned covariates.

Statistical Analysis

The sample size calculation was based on the past literature with the same population characteristics, such as those included in Cies and Shankar[7] study. In their study, vancomycin-associated AKI was presented in 14% (95% CI: 7%–21%) of patients. We calculated that with a 95% CI and 6.5% precision (based on the 7%–21% interval), the study would require 110 patients to estimate the proportion of patients with vancomycin-related AKI in PICU.

Continuous variables were expressed by mean or median and dispersion statistics [SD and interquartile range (IQR)]. Categorical variables were reported as counts and percentages. Independent covariates were included one-by-one in a univariate model using GEEs. Covariates that were able to predict ($P \leq 0.2$) pRIFLE classification worsening were included in a multivariate model.

Last, data were hierarchically and progressively included in the multivariate model, through defined blocks, such as demographics, vancomycin-related variables, nephrotoxic drugs, and other clinical data. Variables were maintained in the model if they presented $P < 0.05$. Results were reported as OR and 95% CI interpretations. GEE results were interpreted as an ordinal regression, which means that when OR > 1, there is an increased odds that a covariate is associated with worse pRIFLE scores. On the other hand, when OR < 1, the covariate is associated with better pRIFLE classification (clinically better).

RESULTS

Of 236 initially eligible patients receiving vancomycin during the study period, 126 were excluded due to: vancomycin initiation before PICU admission (46%); prophylactic use (34%); and the presence of renal damage or elevated SCr values by the time vancomycin was started (20%).

The study included 110 patients, representing 1177 vancomycin days. Most of the patients were male (53.6%) with a median age of 16 (IQR: 6–70) months. More than half of the population were admitted to PICU with respiratory failure (58.2%), with median PIM2 score of 3.9 (IQR: 3.9–11.47). By the time vancomycin was started, the median SCr and eCC was, respectively: 0.3 (IQR: 0.23–0.4) mg/dL and 127.16 (IQR: 91.3–158.3) mL/min/1.73 m2 (Table 1).

In 77.3% of the cases, vancomycin was empirically used, without an identified microorganism. The median initial vancomycin dose was 57.7 (IQR: 41.7–61.5) mg/kg/day, while the median serum concentration was 10 (IQR: 6.4–18.4) mg/L. The median treatment duration was 12 (IQR: 9–14) days, and 8 (12.7%) patients were treated for more than 20 days.

Nephrotoxicity occurred in 13 children (11.8%) and the final SCr at the end of vancomycin therapy was 0.3 (IQR: 0.25; 0.41) mg/dL. The most commonly prescribed medications that could contribute with an increased risk for nephrotoxicity included: vasoactive drugs (66.4%) and diuretics, such as furosemide (70.9%). The 28-day mortality rate was 13.6% (15 patients), where 5 of them developed AKI during vancomycin therapy.

TABLE 1. Baseline Patient Characteristics

Demographics	
All patients	n = 110
Sex, n (%)	
Male	59 (53.64%)
Female	51 (46.36%)
Age, months, median (IQR)	15.5 (6.00; 70.25)
Weight, kg, median (IQR)	9.35 (5.5; 9.3)
Height, cm, median (IQR)	74.75 (52.75; 102.87)
Cause of hospital admission	
Respiratory disease	64 (58.2%)
Neurologic disease	5 (4.5%)
Cancer/hematologic disease	1 (0,9%)
Gastrointestinal/liver disease	10 (9.1%)
Shock	18 (16.4%)
Others	12 (10.9%)
Coexisting condition at baseline	
No comorbidities	30 (27.3%)
Respiratory disease	11 (10%)
Neurologic disease	16 (14.5%)
Cancer/hematologic disease	16 (14.5%)
Gastrointestinal/liver disease	17 (15.5%)
Metabolic disorder	9 (8.2%)
Cardiovascular disease	4 (3.6%)
Others	7 (6.4%)
PICU related	
PIM2, in %, median (IQR)	3.9 (3.9; 11.47)
Renal excretion related	
Baseline SCr (mg/dL), median (IQR)	0.3 (0.23; 0.4)
Baseline eCC (mL/min/1.73m2), median (IQR)	127.16 (91.33; 158.32)
Use of nephrotoxins	
Vasoactives	73 (66.4%)
ACE Inhibitor	2 (1.8%)
Acyclovir	10 (9.1%)
Amikacin	6 (5.5%)
Amphotericin B	7 (6.4%)
Cyclosporine	2 (1.8%)
Ganciclovir	6 (5.5%)
Piperacillin and tazobactam	14 (12.7%)
Polymyxin B	4 (3.6%)
Tacrolimus	6 (5.5%)
Use of diuretics	
Furosemide	78 (70.9%)
Spironolactone	46 (41.8%)
Hydrochlorothiazide	16 (14.5%)
Antibiotic indication, n (%)	
Empiric/fever	85 (77.3%)
Guided therapy	25 (22.7%)
Vancomycin related	
Vancomycin initial daily dose (mg/kg), median (IQR)	57.7 (41.7; 61.5)
Dose in mg per kg, median (IQR)	14 (11; 15)
Doses with serum levels ≥ 15 mg/L*	235 (45%)
Vancomycin initial trough (mg/L), median (IQR)	10 (6.38; 18.42)
Duration of vancomycin therapy (days), median (IQR)	12 (9; 14)

*The denominator was 523 (total vancomycin serum levels).

ACE, angiotensin-converting enzyme; eCC, estimated creatinine clearance; IQR, interquartile range; PICU, pediatric intensive care unit; PIM2, pediatric index of mortality II; SCr, serum creatinine.

Descriptive statistics were reported as absolute numbers and percentages, unless otherwise stated (eg, median and IQR).

In univariate analysis (Table 2), predictors of AKI were: (1) shock by the time they were admitted to PICU; (2) presence of comorbidities (respiratory, neurological, metabolic, and cardiovascular diseases); (3) vancomycin doses (in mg/kg/day); (4) vancomycin serum levels; (5) use of acyclovir, amikacin, amphotericin B, and polymyxin B (nephrotoxins); and (6) furosemide administration.

Table 2. Univariate Analysis With GEE

Variable	n	*P*	OR	95%CI Lower	95%CI Upper
Sex					
Male	59	0.392	1.353	0.677	2.707
Female	51	—	Ref	—	—
Age	110	0.588	0.998	0.991	1.005
Weight	110	0.834	1.003	0.978	1.027
Height	110	0.811	0.999	0.988	1.010
Pediatric index of mortality II	110	0.762	1.002	0.990	1.014
Cause of admission					
Respiratory disease	64	0.330	0.458	0.095	2.202
Neurologic disease	5	0.822	1.320	0.117	14.874
Oncologic/Hematologic	1	0.012	0.141	0.031	0.648
Gastrointestinal/liver disease	10	0.940	1.081	0.139	8.426
Shock*	18	0.067	0.221	0.044	1.113
Others	12	—	Ref	—	—
Coexisting condition at baseline					
No comorbidities	30	0.263	0.308	0.039	2.418
Respiratory disease	11	0.078	0.127	0.013	1.256
Neurologic disease	16	0.193	0.236	0.027	2.081
Cancer/hematologic disease	16	0.083	0.15	0.018	1.28
Gastrointestinal/liver disease	17	0.275	0.287	0.03	2.703
Metabolic disorder	9	0.065	0.133	0.016	1.133
Cardiovascular disease	4	0.147	0.166	0.015	1.88
Others	7	—	Ref	—	—
Antibiotic indication					
Empiric/fever	85	0.938	1.035	0.440	2.434
Guided therapy	25	—	Ref	—	—
Renal excretion related					
SCr (mg/dL)*	110	<0.000	0.002	0.000	0.017
eCC (mL/min/1.73 m2)*	110	<0.000	1.059	1.041	1.077
Dialysis					
No dialysis*	106	<0.000	26.896	7.121	101.593
Peritoneal dialysis	2	0.304	2.036	0.525	7.892
Hemodialysis	2	—	Ref	—	—
Vancomycin related					
Dose in mg per kg	110	0.965	0.998	0.927	1.075
Frequency of vancomycin dose*	110	0.006	1.708	1.162	2.511
Vancomycin daily dose (mg/kg)*	110	0.082	1.015	0.998	1.033
Vancomycin trough (mg/L)*	110	0.026	0.966	0.936	0.996
Use of nephrotoxins					
Vasoactives					
No	37	0.782	0.869	0.321	2.351
Yes	73	—	Ref	—	—
Acyclovir*					
No	100	<0.000	4.339	3.168	5.943
Yes	10	—	Ref	—	—
Amikacin*					
No	104	0.074	2.044	0.934	4.476
Yes	6	—	Ref	—	—
Amphotericin B*					
No	103	0.007	5.542	1.586	19.366
Yes	7	—	Ref	—	—
Cyclosporine					
No	108	0.916	0.906	0.144	5.695
Yes	2	—	Ref	—	—
Piperacillin and tazobactam					
No	96	0.486	4.502	0.066	309.058
Yes	14	—	Ref	—	—
Polymyxin B*					
No	106	0.065	4.687	0.910	24.136
Yes	4	—	Ref	—	—
Use of diuretics					
Furosemide*					
No	32	<0.000	2.479	1.620	3.796
Yes	78	—	Ref	—	—
Spironolactone					
No	64	0.232	2.247	0.595	8.482
Yes	46	—	Ref	—	—
Hydrochlorothiazide					
No	94	0.449	1.828	0.383	8.724
Yes	16	—	Ref	—	—

*Variables with *P* values ≤ 0.2 in univariate GEE were considered for a multivariate model.

CCe, estimated creatinine clearance; IQR, interquartile range; PICU, pediatric intensive care unit; PIM2, pediatric index of mortality II; SCr, serum creatinine.

TABLE 3. Multivariate Analysis With GEE

Variable	n	*P*	OR	95%CI Lower	95%CI Upper
Coexisting condition at baseline					
Metabolic disorder	9	0.302	2.229	0.486	10.223
No comorbidities	30	—	Ref	—	—
Vancomycin related					
Frequency of vancomycin dose*	110	0.002	0.428	0.250	0.734
Vancomycin daily dose (mg/kg)	110	0.640	1.005	0.985	1.026
Vancomycin trough (mg/L)*	110	<0.000	1.045	1.019	1.071
Use of nephrotoxins					
Acyclovir					
No	100	—	Ref	—	—
Yes	10	0.164	2.205	0.725	6.710
Amphotericin B*					
No	103	—	Ref	—	—
Yes	7	<0.000	7.709	2.552	23.292
Polymyxin B					
No	106	—	Ref	—	—
Yes	4	0.589	0.744	0.254	2.18
Use of diuretics					
Furosemide*					
No	32	—	Ref	—	—
Yes	78	0.003	2.563	1.377	4.769

*P values <0.05 were considered statistically significant.

In the multivariate model, vancomycin doses had no association with worse renal function (pRIFLE). The addition of furosemide and/or amphotericin B to the vancomycin treatment was highly associated with renal function deterioration [OR of 2.56 (95% CI: 1.38–4.8) and 7.7 (95% CI: 2.55–23), respectively] (Table 3).

DISCUSSION

In this study, nephrotoxicity was identified in 11.8% of critically ill children receiving vancomycin, without preexisting renal injury. That is, by adopting this criterion, 20% of children were excluded due to elevated eCC in the baseline period, and might have reduced an important source of confounding. This is corroborated by previous studies, which reported a range of 17%–23.4% of vancomycin-related AKI in critically ill children.[8,11–15] The 17% value accounted for studies that included PICU patients without preexisting renal injury,[8] while 23% was found in studies that did not control for baseline renal function.[6]

One meta-analysis[16] of 15 studies that evaluated only critically ill patients (one report was about pediatric population) concluded that vancomycin-related nephrotoxicity was associated with high serum levels (≥15 mg/L, OR = 2.6). Another recent systematic review[11] and 2 other studies[2,3] reported similar ORs (2.2–2.5) to describe the association between AKI and vancomycin serum levels of more than 15 mg/L.

In our study, 45% of vancomycin serum levels were ≥15 mg/L. In the multivariate model, the association between high serum levels (≥15 mg/L) and worse pRIFLE scores was weaker (OR: 1.05, 95% CI: 1.02–1.07) than previous studies.[2,3,11] Conversely, we found 3 studies that showed no association between elevated trough concentrations and AKI.[5,8,17] We attribute these differences due to the use of different tools to assess AKI.[2,3,5,8,11] We measured renal injury with pRIFLE, which is a method that uses eCC instead of solely SCr; thus, it is clinically more relevant and sensitive for detecting AKI[11] in hypovolemia states.

Another hypothesis that explains the difference on vancomycin use and AKI association relies on the presence of risk factors for renal injury. Few studies have concluded that patients on concomitant use of vancomycin and furosemide were more likely to develop AKI: OR = 9.45 (95% CI: 3.44–26.00),[4] OR = 2.23 (95% CI: 1.27–3.93),[8] and OR = 3.52 (95% CI: 1.88–6.62).[6] These results are consistent with our findings, where only furosemide was associated with worse pRIFLE scores (OR: 2.56, 95% CI: 1.38–4.8).

Importantly, critically ill patients have several AKI risk factors. Renal injury is multifactorial and can be caused by decreased renal perfusion, multiple organ dysfunction, and sepsis.[13] Unfortunately, the hemodynamic and volemia impact on renal function, and its association with vancomycin-induced nephrotoxicity cannot be easily interpreted or studied.[18,19]

Despite renal injury is a prevalent and serious event in PICU, we observed that vancomycin-related AKI was reversible, likewise reported by previous authors.[6–8] The final SCr was 0.3 mg/dL (IQR: 0.25; 0.41), the same SCr baseline value.

Our study has limitations due to the retrospective design and single institution recruitment. Thus, the results should be carefully interpreted and more studies considering patients without AKI during the initiation of vancomycin and the use of pRIFLE are warranted to confirm our findings.

CONCLUSION

In critically ill patients, vancomycin-associated nephrotoxicity was seen in 11.8%, corroborating with past studies that included children without preexisting renal injury by the time vancomycin therapy was started, and pRIFLE was used as a renal function assessment tool. By not using the aforementioned inclusion criteria, the number of patients with AKI would be 20% higher.

Out of 3 risk factors found to be associated with worse pRIFLE scores, 2 are related with hemodynamic status and volemia (vancomycin concentration levels and furosemide). Finally, vancomycin-associated AKI was reversible in our study, suggesting that the renal injury was not worsened by drug. Further research should be conducted using the same inclusion criterion (pRIFLE tool for renal function assessment and inclusion of patients without preexisting AKI) to standardize future comparisons. There is also a need to understand what factors contribute more with AKI: the clinical condition (infection), other nephrotoxic drugs, or vancomycin.

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