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Impact of an Antibiotic Stewardship Program on the Incidence of Vancomycin-Associated Acute Kidney Injury in Hospitalized Children

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OBJECTIVE Vancomycin causes considerable acute kidney injury (AKI) in children, particularly in the setting of troughs of 15 to 20 mg/L. We sought to determine whether the addition of prospective audit and feedback to a preauthorization and therapeutic drug monitoring (TDM) program further reduces the incidence of AKI.

METHODS We conducted a quasiexperimental study of children admitted to The Johns Hopkins Hospital receiving vancomycin for ≥48 hours. The incidence of AKI was compared between the preintervention and intervention periods. Additional risk factors for vancomycin-associated AKI were also explored.

RESULTS A total of 386 courses of vancomycin therapy met eligibility criteria (200 in the preintervention vs 186 in the intervention period). The incidence of vancomycin-associated AKI did not differ between the preintervention and intervention periods, 8% vs 9%, respectively. On multivariable analysis, the number of concurrent nephrotoxins was found to be an independent predictor of vancomycin-associated AKI, with each additional nephrotoxin increasing the risk of AKI by 40% (adjusted OR, 1.40; 95% CI, 1.06–1.85; p = 0.019). Specific nephrotoxins that increased the risk of vancomycin-associated AKI included piperacillin/tazobactam, liposomal amphotericin B, and ibuprofen.

CONCLUSION The addition of prospective audit and feedback to a preauthorization and TDM program did not result in further AKI reduction. Prospective audit and feedback is a resource-intensive intervention. If preauthorization restrictions and TDM are already in place, our findings suggest stewardship efforts may be more effective if redirected to focus on other modifiable risk factors for vancomycin-associated AKI, such as minimizing additional nephrotoxins.

ABBREVIATIONS AKI, acute kidney injury; ASP, antibiotic stewardship program; CrCl, creatinine clearance; MRSA, methicillin-resistant *Staphylococcus aureus*; pRIFLE, Pediatric Risk, Injury, Failure, Loss, End stage renal disease; TDM, therapeutic drug monitoring

KEYWORDS acute kidney injury; antimicrobial stewardship; pediatrics; vancomycin

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Introduction

Vancomycin has the potential to cause considerable acute kidney injury (AKI) in children, particularly when vancomycin troughs of 15 to 20 mg/L are targeted for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[1] A previous study conducted at our institution identified a baseline AKI incidence of 14% between the years of 2009 and 2010[2] using the Pediatric Risk, Injury, Failure, Loss, End stage renal disease (pRIFLE) criteria[3] of at least a 50% decline in estimated creatinine clearance (CrCl). After implementing higher vancomycin trough targets within our institution in 2010, we were concerned that the frequency of vancomycin-associated AKI in children would increase.

Although antibiotic stewardship programs (ASPs) have proven successful in reducing antibiotic use, there are limited data on their impact on patient safety. Therefore, we conducted daily prospective audit and feedback for all children receiving vancomycin to determine if this could result in further reductions in the incidence of vancomycin-associated AKI in hospitalized children.

Materials and Methods

Study Design. We conducted a quasiexperimental study of children admitted to The Johns Hopkins Hospital treated with intravenous vancomycin for at least 48 hours from February 2015 through January 2016. Children were excluded if they had a baseline CrCl <60 mL/min/1.73 m^2 as estimated by the Bedside CKiD equation,[4] were receiving renal replacement therapy, or were requiring extracorporeal membrane oxygenation. During the intervention period (August 2015 to January 2016), the ASP pharmacist performed prospective audit and feedback for all children receiving vancomycin. Au-

dits occurred on a daily basis Monday through Friday to determine if vancomycin was indicated. If interventions were necessary, the recommendations were provided by the ASP team to the prescriber.

Cultures were considered negative if no growth was observed by 48 hours. During the preintervention period (February 2015 to July 2015), no vancomycin prospective audit and feedback was performed. Existing ASP and clinical pharmacy efforts that remained constant throughout the preintervention and intervention periods included: 1) preauthorization restrictions for vancomycin use, 2) vancomycin dosing and therapeutic drug monitoring (TDM) guidelines, and 3) clinical pharmacokinetics service provided by credentialed clinical pharmacists 24/7. Our preauthorization program consists of pediatric infectious diseases fellows covering the antibiotic approval pager from 9:00 am until 10:00 pm, 7 days per week. During overnight hours, most restricted antibiotics are automatically released, and then reviewed the subsequent morning by a pediatric infectious diseases fellow. Our clinical pharmacists provide vancomycin TDM recommendations 24/7 after assessing the timing of doses and levels, target trough goals, and renal function.

Data Collection. Patient demographics, preexisting medical conditions, renal function, concurrent nephrotoxins, vancomycin levels, and dates and timing of vancomycin administration were manually extracted from the medical records. The indications for vancomycin therapy and target trough ranges were determined by review of daily progress notes and pharmacokinetic consult notes. Any interventions made by the ASP team were documented (e.g., discontinue vancomycin, change to alternative agent, target lower/higher trough based on indication). Time to intervention acceptance was also documented. This study was reviewed and approved by the Institutional Review Board at The Johns Hopkins Hospital, with a waiver of informed consent.

Definitions. One day of vancomycin therapy was defined as 1 calendar day during which at least 1 dose of vancomycin was administered. A vancomycin trough was defined as a concentration obtained within 60 minutes of the next scheduled dose, with appropriate timing of each previous dose (defined as no more than a 2-hour deviation from the scheduled time of administration). Steady-state trough concentrations were defined as troughs obtained before at least the fourth dose of the same vancomycin regimen. AKI was defined as at least a 50% decline in CrCl from baseline anytime during and up to 72 hours after vancomycin therapy completion.[3] Concurrent nephrotoxins were defined as the use of any of the nephrotoxic agents listed in a publication by Goldstein and colleagues[5] 72 hours before, during, and up to 72 hours after vancomycin therapy completion.

Statistical Analysis. Baseline characteristics were compared using the Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. Logistic regression was used to estimate the odds of developing AKI. All analyses were performed using Stata 15.1 (StataCorp LP, College Station, TX). A 2-sided p value of <0.05 was used to determine statistical significance.

Results

During the 12-month study period, 657 vancomycin courses were reviewed, of which 386 courses met eligibility criteria (200 in the preintervention vs 186 in the intervention period). Reasons for exclusion were duration of therapy <48 hours (n = 142), CrCl <60 mL/min/1.73 m^2 (n = 116), renal replacement therapy (n = 10), and extracorporeal membrane oxygenation (n = 3).

Patient Population. Baseline characteristics are outlined in Table 1 and were generally similar between both periods. There was a lower proportion of intensive care unit admissions in the preintervention vs intervention period (45% vs 58%). The most common empiric indications for vancomycin were sepsis rule outs (50%), central nervous system infections (13%), and skin and soft tissue infections (11%). There was a similar proportion of concurrent nephrotoxins in both periods (66% vs 63%), with the most common nephrotoxins being intravenous contrast, trimethoprim/sulfamethoxazole, piperacillin/tazobactam, ibuprofen, gentamicin, acyclovir, and liposomal amphotericin B. The proportion of patients receiving 3 or more concurrent nephrotoxins was similar between both periods, 13% vs 15%.

The median duration of vancomycin therapy was 3 days (IQR, 2–4 days) in both periods. The proportion targeting higher troughs of 15 to 20 mg/L was similar in both groups at 29% and 26% in the preintervention and intervention periods, respectively. The median (IQR) trough during the entire course of vancomycin therapy was higher in the preintervention vs intervention period, 12 (10–16) vs 10 (8–14) mg/L, respectively (p = 0.004). The proportion of children with supratherapeutic troughs ≥20 mg/L at any point in time during vancomycin therapy was similar between the preintervention and intervention periods (14% vs 13%; p = 0.868).

ASP Interventions During Prospective Audit and Feedback Period. During the 6-month intervention period, the ASP team intervened on 36% of vancomycin orders reviewed. The most common recommendation—made in 80% of cases—was to discontinue vancomycin. Other interventions included switching to an alternative agent (12%), targeting a lower vancomycin trough range (5%), and targeting a higher vancomycin trough range (3%). The proportion of interventions accepted by day 3 of vancomycin therapy was 55%.

Incidence of Vancomycin-Associated AKI and Description of Children with AKI. The proportion of children receiving vancomycin who developed AKI did not differ between the preintervention and intervention periods, 8% vs 9%, respectively; unadjusted OR, 1.11;

Table 1. Baseline Characteristics of Hospitalized Children Receiving Vancomycin Prior to and During a Vancomycin Prospective Audit and Feedback Intervention

	Preintervention Period (n = 200)	Intervention Period (n = 186)	p value
Age, yr, median (IQR)	7.6 (1.6–15.7)	5.9 (0.5–14.6)	0.081
Male sex, n (%)	111 (55.5)	102 (54.8)	0.919
Serum creatinine on day 1 of vancomycin, mg/dL, median (IQR)	0.4 (0.2–0.5)	0.3 (0.2–0.6)	0.857
Creatinine clearance on day 1 of vancomycin 60 to <75 mL/min/1.73 m^2, n (%)	20 (10)	22 (11.8)	0.625
Preexisting medical conditions, n (%)			
None, previously healthy	30 (15)	30 (16.1)	0.780
Immunocompromised*	71 (35.5)	69 (37.1)	0.752
Cardiovascular disease	24 (12)	14 (7.5)	0.172
Structural lung disease	28 (14)	34 (18.3)	0.270
Intestinal insufficiency	6 (3)	7 (3.8)	0.781
Other condition	76 (38)	56 (30.1)	0.108
Vancomycin trough target of 15–20 mg/L, n (%)	57 (28.5)	48 (25.8)	0.569
ICU admission, n (%)	90 (45)	107 (57.5)	0.015
Any concurrent nephrotoxin 72 hr before, during, and up to 72 hr after vancomycin therapy, n (%)	132 (66)	118 (63.4)	0.670
3 or more concurrent nephrotoxins, n (%)	26 (13)	28 (15.1)	0.660
Concurrent nephrotoxins, n (%)			
Acyclovir	19 (9.5)	13 (7)	0.461
Gentamicin	22 (11)	12 (6.5)	0.150
Liposomal amphotericin B	11 (5.5)	10 (5.4)	1.000
Ibuprofen	17 (8.5)	19 (10.2)	0.602
Piperacillin/tazobactam	26 (13)	28 (15.1)	0.660
Trimethoprim/sulfamethoxazole	33 (16.5)	35 (18.8)	0.594
Intravenous contrast	42 (21)	49 (26.3)	0.232
Other†	63 (31.5)	49 (26.3)	0.312

ICU, Intensive Care Unit

* Immunocompromised includes neutropenia, chemotherapy within 6 mo, hematopoietic stem cell transplantation within 12 mo, solid organ transplantation, and receipt of immunomodulators including >14 days of systemic corticosteroids.

† Each of the following nephrotoxins were <5% in each arm: amikacin, tobramycin, amphotericin B deoxycholate, captopril, cefotaxime, ceftazidime, cefuroxime, cidofovir, cyclophosphamide, enalapril, fludarabine, ganciclovir, ketorolac, lisinopril, lithium, methotrexate, sirolimus, tacrolimus, topiramate, valacyclovir, valganciclovir, voriconazole, zonisamide.

95% CI, 0.52 to 2.34; p = 0.787. Children who developed AKI were more likely to be mechanically ventilated (57% vs 34%; p = 0.017), receive longer median durations of vancomycin therapy (4 [IQR, 2–8)] vs 3 [IQR, 2–4] days, p = 0.048), and receive a higher median number of concurrent nephrotoxins (1.5 [IQR, 1–3] vs 1 [IQR, 0–2], p = 0.032) compared with children who did not develop AKI. There was no difference between children who developed AKI vs those who did not develop AKI with respect to presence of baseline CrCl 60 to <75 mL/min/1.73 m^2. The median trough during the first 72 hours of vancomycin therapy was similar between children who developed AKI vs children who did not, 10 (IQR, 8–14) vs 11 (IQR, 8–15) mg/L, respectively, p = 0.884. There was also no difference between the 2 groups with respect to the proportion of children with supratherapeutic troughs ≥20 mg/L within the first 72 hours of therapy (13% vs 9%; p = 0.467).

Risk Factors for Vancomycin-Associated AKI. On univariable analysis, each additional day of vancomycin therapy increased the odds of AKI by 7% (OR, 1.07; 95% CI, 1.01–1.13; p = 0.013; Table 2). Each additional nephrotoxin increased the odds of AKI by 35% (OR, 1.35; 95% CI, 1.06–1.72; p = 0.014). Specific combinations of nephrotoxins that were associated with AKI included vancomycin plus piperacillin/tazobactam (OR, 2.72;

Table 2. Univariable and Multivariable Analysis of Risk Factors for Vancomycin-Associated Acute Kidney Injury

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Intervention period	1.11 (0.52–2.34)	0.787	0.91 (0.42–2.00)	0.822
Age, yr	0.98 (0.93–1.03)	0.341		
CrCl 60 to <75 mL/min/1.73 m^2 at baseline	0.24 (0.03–1.84)	0.171		
Immunocompromised	1.07 (0.50–2.30)	0.860		
ICU admission	1.44 (0.67–3.08)	0.350		
Vasopressors	1.68 (0.71–3.95)	0.237		
Mechanical ventilation	2.52 (1.18–5.38)	0.017	3.21 (1.41–7.27)	0.005
Any concurrent nephrotoxin	2.19 (0.87–5.50)	0.096		
Days of vancomycin therapy	1.07 (1.01–1.13)	0.013	1.05 (0.99–1.12)	0.097
No. of concurrent nephrotoxins	1.35 (1.06–1.72)	0.014	1.40 (1.06–1.85)	0.019
Trough concentration ≥20 mg/L within first 72 hr	1.49 (0.41–5.39)	0.546		

CrCl, creatinine clearance

* The following variables were included in the adjusted analysis: intervention period, mechanical ventilation, duration of vancomycin therapy, and the number of concurrent nephrotoxins.

95% CI, 1.17–6.32; p = 0.020), vancomycin plus liposomal amphotericin B (OR, 3.94; 95% CI, 1.33–11.64; p = 0.013), and vancomycin plus ibuprofen (OR, 3.06; 95% CI, 1.14–8.18; p = 0.026). Mechanical ventilation was also associated with an increased odds of AKI (OR, 2.52; 95% CI, 1.18–5.38; p = 0.017).

On multivariable analysis, after controlling for intervention period, duration of vancomycin therapy, and mechanical ventilation, the number of concurrent nephrotoxins was found to be an independent predictor of vancomycin-associated AKI, with each additional nephrotoxin increasing the risk of AKI by 40% (adjusted OR, 1.40; 95% CI, 1.06–1.85; p = 0.019; Table 2). Mechanical ventilation also remained an independent predictor of vancomycin-associated AKI on multivariable analysis (adjusted OR, 3.21; 95% CI, 1.41–7.27; p = 0.005).

Discussion

We were unable to demonstrate an added benefit with implementing prospective audit and feedback on top of a well-established preauthorization program with restrictions for vancomycin use coupled with a pharmacokinetics service staffed 24/7 by clinical pharmacists. The pharmacokinetics service provides a mechanism for daily reassessment of vancomycin indication, dosing, and levels after initial vancomycin approval. We did, however, find that the receipt of concurrent nephrotoxins increased the odds of developing AKI, particularly piperacillin/tazobactam, liposomal amphotericin B, and ibuprofen. Furthermore, each additional nephrotoxin increased the odds of vancomycin-associated AKI by 40%.

A previous study in adults demonstrated significantly lower rates of AKI after implementation of an ASP.[6,7] It was a retrospective study that was conducted in 453 adults at a Veterans Affairs hospital and nephrotoxicity was defined as a rise in serum creatinine of at least 0.5 mg/dL or increase by 50% from baseline for 2 consecutive days. The ASP incorporated a number of interventions including preauthorization, prospective audit and feedback, and TDM that consisted of the stewardship pharmacist ordering vancomycin levels and adjusting vancomycin dosages.[6] The incidence of nephrotoxicity was significantly reduced from 14% to 8% after the intervention.[6,7] In contrast to our study, the adult study measured the impact of all 3 of these interventions together. In our institution, vancomycin TDM guidelines and clinical pharmacokinetic services predated the current intervention, which may explain the limited additive value of prospective audit and feedback that we observed.

In our study, each additional day of vancomycin therapy increased the odds of AKI by 7%, although this did not remain significant on multivariable analysis. Other studies have also shown an incremental increase in nephrotoxicity associated with longer durations of vancomycin therapy.[8] We believe this underscores the importance of developing local antibiotic guidelines that clarify when empiric vancomycin is warranted and stress discontinuation of vancomycin when organisms such as MRSA have not been isolated. Negative MRSA surveillance swabs have a high negative predictive value for ruling out MRSA pneumonia, and may assist with efforts to discontinue vancomycin therapy.[9] Another potential area for improvement is to decrease concurrent antimicrobials known to incite nephrotoxicity in patients receiving vancomycin, particularly piperacillin/tazobactam and amphotericin B. The combination

of vancomycin plus piperacillin/tazobactam has been found to be associated with a higher odds of AKI in both children[10] and adults.[11] In our study, the risk of AKI was 2.7-fold higher with the addition of piperacillin/tazobactam to vancomycin.

Our study has several limitations. Data collected prospectively from the 6-month intervention period were compared to data collected retrospectively from the 6-month preintervention period; these were non-concurrent cohorts. The acceptance rate of our interventions was only 55% by day 3 of vancomycin therapy. We attempted to explore if patients who were successfully intervened upon had a decreased likelihood of AKI, but small numbers precluded a meaningful analysis of this question. Our results might not be applicable to interventions resulting in higher acceptance rates and subsequently less vancomycin use. Our AKI definition did not include the urine output criteria that is included in the pRIFLE criteria because of the difficulty in retrospectively abstracting this information accurately from the medical records, which potentially limits the precision of our AKI classification. Prospective audit and feedback was not conducted 7 days a week; therefore, there was some lost opportunity for intervention, which may have adversely affected our results. Lastly, our sample size was small, potentially limiting our power to detect a difference in AKI, if one existed.

Conclusions

The results of our study suggest there may not be an additional benefit of implementing targeted vancomycin prospective audit and feedback on top of a well-established preauthorization program coupled with a clinical pharmacokinetics service staffed 24/7. These data are informative because prospective audit and feedback is a resource-intensive stewardship intervention, and if preauthorization restrictions and TDM of vancomycin are already in place, efforts may be most effective if redirected to focus on other modifiable risk factors for vancomycin-associated AKI, such as minimizing the use of additional nephrotoxic agents, such as piperacillin/tazobactam.

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