Clinical Outcomes and Resource Utilization in Children Who Develop Acute Kidney Injury Following Vancomycin Use for Treatment of MRSA Bacteremia and Acute Hematogenous Osteomyelitis

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ABSTRACT

Background
Vancomycin is recommended for treatment of acute hematogenous osteomyelitis (AHO) with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, despite the risk of nephrotoxicity. This study evaluates the rate of vancomycin associated acute kidney injury (AKI) and assesses resource utilization and cost for children admitted with AHO and MRSA bacteremia.
Methods
Children who received vancomycin for a sufficient duration to have at least one trough level drawn from 2009 to 2019 were retrospectively studied. AKI was assessed by chart review and Kidney Disease Improving Global Outcomes (KDIGO) criteria. Cohorts of children with and without KDIGO AKI were compared based on severity of illness, treatment, resource utilization, and outcomes. Multivariate analysis evaluated risk factors for AKI. Cost analysis was performed using institutional data and the Pediatric Health Information System (PHIS) database.
Results
Eighty-five children met inclusion criteria. Of these, 14 (16.5%) had chart documented AKI, whereas 24 (28.2%) met KDIGO criteria. There were no differences between cohorts based on initial creatinine, severity of illness, or duration of bacteremia. Children with AKI had more febrile days (median 5.5d vs 3d) and higher rates of thrombosis (median 41.7% vs 18%). They also had significantly higher maximum vancomycin trough concentration (VTC; median 27.8 vs 17.5 mg/L) and longer vancomycin duration (median 8 vs 5 d). The AKI group had more creatinine levels, vancomycin troughs, and hospital days (median 19.9 vs 11.1 days). Multivariate analysis revealed maximum VTC (Odds Ratio 1.05; threshold 21.7 mg/L) to be a significant predictor of AKI (p=0.003). Estimated total charges for 24 children with vancomycin associated AKI exceeded that of the non-AKI cohort by $1.6M.
Conclusions
Provider documented AKI grossly underestimated that determined by KDIGO criteria. Vancomycin associated AKI results in significant increases in resource utilization and healthcare costs. A high VTC>21.7 mg/dL is a significant contributing factor to AKI.

BACKGROUND

- Children with AHO due to MRSA often have severe illness[1-2] and require an integrated approach to optimize treatment and reduce the risk of adverse outcomes.
- Parenteral vancomycin is recommended for the treatment of children hospitalized with AHO and concurrent MRSA bacteremia. [3-4, 12] However, slow bactericidal activity[5], poor bone penetration[6], and potential for nephrotoxicity are concerns regarding vancomycin use. Additionally, substantial effort is expended by pediatric hospitalists and intensivists, including frequent laboratory monitoring of renal function and therapeutic drug levels, to ensure the safe and effective use of vancomycin.[7]
- Nephrotoxicity is a serious complication of vancomycin use. Previous studies demonstrate a 13-27% AKI rate for vancomycin treated children.[8-11] Additional downstream resources such as testing, monitoring, and treatment are often required to address AKI.

OBJECTIVES

The **primary aim** of this study was to evaluate the rate of AKI among children with AHO and MRSA bacteremia who were treated with intravenous vancomycin. The **secondary aim** was to investigate the resource utilization, cost, and risk factors that may impact the occurrence of AKI.

METHODS

Study Population & Outcomes
Children 0-18 years old with AHO and MRSA bacteremia from January 1, 2009, to December 31, 2019, were retrospectively studied. They had to be treated with vancomycin for a duration sufficient to have at least one vancomycin trough drawn. Exclusion criteria were immunocompromise, history of penetrating inoculation and surgical site infection.

Review of chart documentation was performed to identify provider-perceived occurrence of AKI. Separately, the KDIGO criteria of increase in creatinine ≥0.3 mg/dL or ≥50% from baseline after initiation of vancomycin therapy with no alternative explanation was used to objectively identify AKI occurrence. Comparison cohorts were established based on presence or absence of KDIGO AKI.

Statistical Analysis
Statistical significance was established at p<0.05. Multivariate binary logistic regression analysis was performed to identify factors associated with risk for AKI.

Cost Analysis
Institutional data were used to calculate costs of laboratory monitoring associated with vancomycin use. Data from the PHIS database were retrieved for cost analysis of vancomycin-associated AKI. PHIS is an administrative and billing database containing encounter-level data from 49 tertiary care pediatric hospitals affiliated with the Children's Hospital Association in the United States. Children aged 0-18 years who were hospitalized between January 1, 2000, and December 31, 2019, were included. ICD-9 and ICD-10 codes were used to identify occurrence of AHO and filtered to identify vancomycin treatment. Median length of stay (LOS), charges and ICU admission data were compared between groups with and without AKI.

RESULTS

Table 1. Demographic and Clinical Characteristics with and without AKI by KDIGO Criteria

	No AKI (N = 61)	AKI (N = 24)	p-value
Demographics			
Gender (rate)			
Female	22 (36.1%)	8 (33.3%)	0.812
Male	39 (63.9%)	16 (66.7%)	
Age, med (IQR), years	8.4 (4.3—12.4)	8.6 (5.0—11.8)	0.581
BMI, med (IQR), kg/m^2	18.7 (16.4—21.0)	16.9 (15.0—19.1)	0.134
Illness Severity			
Initial creatinine, med (IQR), mg/dL	0.6 (0.4—0.8)	0.4 (0.3 – 0.7)	0.083
Initial CRP, med (IQR), mg/dL	19.0 (14.2 – 26.3)	20.9 (15.4 – 24.3)	0.682
CRP at 48 hours, med (IQR), mg/dL	17.7 (12.8 – 21.1)	18.1 (13.1 – 24.6)	0.571
CRP at 96 hours, med (IQR), mg/dL	11.7 (6.4 – 18.6)	16.5 (10.8 – 21.9)	0.064
CRP <2.0 mg/dL (days), med (IQR)	14.0 (10.0 – 22.0)	15.0 (11.8 – 27.5)	0.213
Severity of Illness score, med (IQR)	8.0 (5.0 – 8.0)	8.0 (6.8 – 10.0)	0.118
Bacteremia duration, med (IQR), days	3.0 (2.0 –5.0)	4.5 (3.0 – 6.0)	0.071
Febrile days on Abx, med (IQR)	3 (1 – 7)	5.5 (2.8 – 13.0)	0.034
DVT (rate)	11 (18%)	12 (50%)	0.003
SPE or Pneumonia (rate)	11 (18%)	10 (41.7%)	0.023

Table 1. Demographic data and severity of illness of the study cohorts.

Table 2. Comparison of Treatment and Clinical Outcomes with or without AKI by KDIGO Criteria

	No AKI (N = 61)	AKI (N = 24)	p-value
Treatment			
ICU Admission (rate)	22 (36.1%)	10 (41.7%)	0.631
Intubated (rate)	10 (16.4%)	8 (33.3%)	0.085
Vasopressor use (rate)	9 (14.8%)	4 (16.7%)	>0.999
Received NSAIDs (rate)	60 (98.4%)	24 (100%)	>0.999
Received contrast (rate)	44 (72.1%)	21 (87.5%)	0.164
Received loop diuretics (rate)	15 (24.6%)	12 (50%)	0.024
Received aminoglycosides (rate)	3 (4.9%)	2 (8.3%)	0.618
Vanc duration, median (IQR), days	5.0 (2.0 – 8.0)	8.0 (4.8 – 15.3)	0.006
AUC/MIC (initial), med (IQR)	402 (250 – 558)	380 (260 – 511)	0.911
Initial vanc trough, med (IQR), mg/L	9.3 (6.1 – 13.0)	7.5 (6.7 – 10.5)	0.564
Max vanc trough, med (IQR), mg/L	17.5 (12.2 – 23.3)	27.8 (21.1 – 39.9)	0.001
Max vanc trough >20 mg/L (rate)	24 (39.3%)	18 (75%)	0.003
Resource Utilization			
Number of vanc troughs, med (IQR)	4.0 (2.0 – 8.0)	9.5 (5.8 – 14.0)	0.002
Number of Cr levels, med (IQR)	5.0 (2.0 – 10.0)	14.0 (6.0 – 25.5)	0.001
Length of stay, med (IQR), days	11.1 (7.5 – 16.0)	19.9 (13.2 – 63.1)	0.001
Hospital Readmission (rate)	10 (16.4%)	3 (12.5%)	0.751

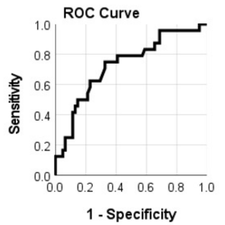
Table 2. Treatment and resources devoted to treatment of cohorts

- 915 creatinine levels ($42,392)
- 648 vancomycin troughs ($62,422)
- 230 vancomycin dosing adjustments

There were 631 children treated for AHO during the study period. Among these, 85 children met inclusion criteria. The majority were male (64.7%) with a median age of 8.4 years. There were 14 (16.5%) children who were recognized to have AKI by the treating team. When KDIGO criteria were applied, 24 (28.2%) children were identified as having AKI, leaving 61 (71.8%) children without AKI in the comparison cohort.

The 85 children had 915 creatinine levels, 648 vancomycin troughs, and 230 vancomycin dosing adjustments during the study period.

Multivariate analysis revealed that maximum VTC (odds ratio (OR) 1.05, p=0.003) with a cutoff of 21.7 mg/L was a significant predictor of AKI. Duration of vancomycin and febrile days on antibiotics did not reach significance in the multivariate model.



Sensitivity	0.75
Specificity	0.67
Cutoff	21.70
AUC	0.73

Figure 1. Receiver operating curve (ROC) for prediction of KDIGO-defined AKI based on vancomycin target concentration (VTC). The area under curve (AUC) of VTCs was 0.73.

RESULTS

Table 3. Patients Treated with Vancomycin for AHO from PHIS Database (2000-2019)

	No AKI (N = 3058)	AKI (N = 75)	p-value
Length of stay, med (IQR), days	7.0 (5.0 – 10.0)	13.0 (9.0 – 20.5)	<0.0001
Days in ICU, med (IQR)	3.0 (1.0 – 6.0)	3.0 (2.0 – 7.5)	0.1763
Pharmacy charges, med (IQR)	$4,611 ($2,436 - $9,533)	$13,324 ($6,544 - $34,944)	<0.0001
Billed charges, med (IQR)	$50,679 ($31,504 - $83,147)	$117,222 ($73,468 - $185,199)	<0.0001

Table 3 demonstrates that vancomycin treated children with AKI had significantly longer LOS, higher pharmacy charges, and higher billed charges than children without AKI in the PHIS database.

The AKI group had median billed charges of $117,222 while the non-AKI group had $50,679. The difference of $66,543 equates to cumulative charge difference of $1.6M between the AKI and non-AKI groups in our institutional study cohort.

CONCLUSIONS

- Vancomycin treatment of MRSA bacteremia and AHO is associated with a significant risk of nephrotoxicity and AKI.
- Clinical diagnosis of AKI (16.5%) grossly underestimated occurrence by KDIGO criteria (28.2%) in this population.
- Significant resource utilization and healthcare costs are associated with the development of AKI in AHO, which may partially be attributed to vancomycin dosing, duration, and therapeutic targets.
- A vancomycin trough >21.7 mg/dL is a significant predictive risk factor for AKI in this setting.

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