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CLINICAL THERAPEUTICS

Effect of Vancomycin-Associated Acute Kidney Injury on Incidence of 30-Day Readmissions among Hospitalized Veterans Affairs Patients with Skin and Skin Structure Infections

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ABSTRACT Among hospitalized adults who received vancomycin for their skin and skin structure infection (SSSI), patients who experienced acute kidney injury (AKI) had considerably higher 30-day readmission rates. Nearly half of the observed 30-day readmissions were due to non-SSSI-related reasons, which is consistent with the persistent organ dysfunction observed among patients with AKI.

KEYWORDS AKI, outcomes, readmissions, vancomycin

Vancomycin is a known cause of acute kidney injury (AKI) (1). For most patients, vancomycin-associated AKI (VA-AKI) is mild and resolves within 1 week after discontinuation of therapy (2). Despite its generally self-limiting nature, VA-AKI has been associated with increased in-hospital mortality, hospital length of stay (LOS), and health care resource utilization (2–7). To date, most studies that assessed the consequences of VA-AKI have focused on outcomes within the index hospitalization, and there are scant data on its longer-term impact (2). Data suggest that AKI is often accompanied by remote organ dysfunction, which increases a patient's susceptibility to a number of conditions (e.g., cardiovascular events, infections due to immunosuppression, etc.) over time (8–11) and may lead to long-term sequela (12). The persistent organ dysfunction or "organ cross talk" is mediated, in large part, by classic uremic stress and its associated sequelae, augmented inflammation, and impairment of immunocompetence that occurs during AKI (8–11). However, the effects of VA-AKI on long-term outcomes like 30-day hospital readmissions have not been thoroughly quantified. The intent of this study was to evaluate the impact of VA-AKI on all-cause, skin and skin structure infection (SSSI)-, and non-SSSI-related 30-day hospital readmission rates among adult hospitalized patients with SSSIs.

The procedures followed for this study were in accordance with the ethical standards of the Helsinki Declaration. The study was approved by expedited review by the Institutional Review Board of Stratton VA Medical Center. A waiver of consent was granted under 45 CFR 46.116(d), and a HIPAA waiver was obtained. To accomplish study objectives, a retrospective cohort study was performed among Veterans' Affairs patients receiving care in the Upstate New York Veterans Healthcare Administration (VISN-2) from 2009 to 2015. Inclusion criteria were as follows: (i) age of ≥18 years, (ii) diagnosis of SSSI based on documentation in medical progress notes, (iii) receipt of vancomycin for ≥48 h, and (iv) vancomycin therapy administered during the first 2 days

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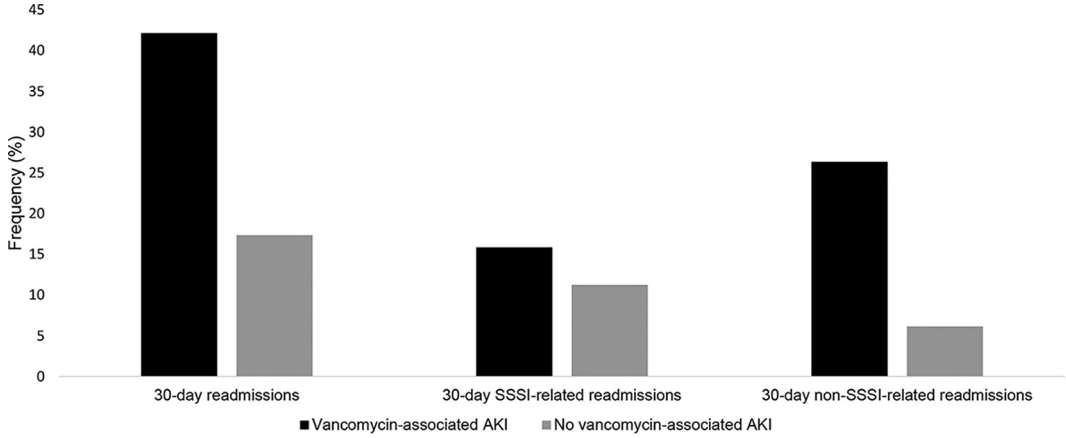

FIG 1 Relationship between vancomycin-associated AKI and 30-day readmissions, stratified by SSSI- and non-SSSI-related admitting diagnoses. The admitting diagnoses for the 17 non-SSSI-related readmissions were heart failure (3 patients), acute renal failure (2 patients), altered mental status (2 patients), venous thromboembolism (2 patients), chronic obstructive pulmonary disorder exacerbation (2 patients), polysubstance abuse (1 patient), hypertensive emergency (1 patient), hospice (1 patient), urinary tract infection (1 patient), non-ST elevated myocardial infarction (1 patient), and orthostasis (1 patient).

of hospitalization. Patients were excluded if they received any renal replacement therapy or died during the index hospitalization.

Data elements collected in this study are listed in Supplemental Text S1. Occurrence of vancomycin-associated AKI was defined as an increase in serum creatinine of 0.5 mg/dl or a ≥50% increase from baseline after 48 h of therapy, whichever was greater (13), after initiation of vancomycin (14). Outcomes assessed included all-cause 30-day readmissions, 30-day SSSI-related readmissions, and 30-day non-SSSI-related readmissions. Hospital readmissions were defined as admission to an inpatient facility for ≥24 h in the 30 days after being discharged from the index hospitalization. For patients who were readmitted, the admitting diagnosis listed in the medical progress note was documented to determine if it was SSSI or non-SSSI related.

Bivariate analyses were performed using chi-square or Fisher's exact tests for categorical variables and Student *t* or Mann-Whitney U tests for continuous variables. Logistic regression analyses were performed to determine if occurrence of vancomycin-associated AKI was independently associated with each study outcome. Variables were eligible for model entry if they were associated with the outcome of interest ($P < 0.25$) in the bivariate analyses and present in at least 5% of the study population. Variables were retained in the model as potential confounders if their removal changed the measure of association for VA-AKI by more than 10%.

During the study period, there were 216 patients who met the study criteria. Most were male (95%), and the mean (standard deviation [SD]) age was 65.1 (12.0) years. Cellulitis was the most common type of SSSI observed (75.9%), and 7.4% of patients had a concomitant bacteremia. The median (interquartile range [IQR]) duration of hospitalization was 7 (5 to 11) days. The median (IQR) acute physiology and chronic health evaluation II (APACHE II) score at initiation of vancomycin therapy was 6 (5 to 10). The median (IQR) duration of vancomycin therapy was 5 (3 to 7) days. There were 189 (87.5%) patients with vancomycin serum concentration data. The median (IQR) highest vancomycin serum concentration within the first 5 days of therapy was 16.0 (11.7 to 20.1) mg/liter. Vancomycin-associated AKI occurred in 19 (8.8%) patients. Among patients experiencing a VA-AKI, the median (IQR) pretreatment serum creatinine was 1.01 mg/dl (0.90 to 1.20), and the worst serum creatinine value on therapy was 2.00 mg/dl (1.6 to 3.1), occurring after a median (IQR) of 5 (4 to 6) days.

Forty-two (19.4%) patients had a 30-day readmission. Most of the readmissions were SSSI related (59.5%). The admitting diagnoses for the non-SSSI-related readmissions are shown in Fig. 1. The proportion of patients with a 30-day readmission was higher in patients with VA-AKI relative to those without VA-AKI (42.1% versus 17.3%; $P = 0.02$)

TABLE 1 Bivariate comparisons of baseline features between vancomycin-associated AKI and non-vancomycin-associated AKI patients and 30-day and non-30-day readmission groups

Parameter	No. (%) with no vancomycin-associated AKI (n = 197)	No. (%) with vancomycin-associated AKI (n = 19)	P value	No. (%) with no 30-day readmission (n = 174)	No. (%) with 30-day readmission (n = 42)	P value
Male sex	187 (94.9)	18 (94.7)	1.00	165 (94.8)	40 (95.2)	1.00
Age (mean ± SD)	64.8 ± 12.6	67.8 ± 11.1	0.30	64.4 ± 12.1	68.0 ± 12.1	0.08
Median weight (kg [IQR])	95.9 (80.2–114.7)	95.0 (75.9–140.2)	0.73	96.2 (80.4–116.5)	90.3 (75.5–111.1)	0.42
Median body mass index (IQR)	30.7 (26.0–37.0)	30.2 (25.8–40.8)	0.81	30.8 (26.2–37.2)	29.5 (23.9–37.6)	0.28
Race						
Caucasian	174 (88.3)	17 (89.5)	0.16	152 (87.4)	32 (92.9)	0.56
Black	17 (8.6)	0 (0)		14 (8.0)	3 (7.1)	
Hispanic	1 (0.5)	0 (0)		1 (0.6)	0 (0)	
Other	5 (2.5)	2 (10.5)		7 (4.0)	0 (0)	
Preadmission location						
Community	139 (70.6)	14 (73.7)	0.82	121 (69.5)	32 (76.2)	0.70
Hospital transfer	24 (12.2)	1 (5.3)		20 (11.5)	5 (11.9)	
Nursing home	10 (5.1)	1 (5.3)		9 (5.2)	2 (4.8)	
Unknown/other	24 (12.2)	3 (15.8)		24 (13.8)	3 (7.1)	
Median baseline creatinine clearance (IQR)	77.0 (58.3–97.1)	72.4 (57.2–101.1)	0.94	77.4 (59.4–100.0)	70.0 (53.1–96.3)	0.44
Median APACHE II score at initiation of vancomycin therapy (IQR)	6 (5–10)	7 (5–10)	0.31	6.0 (5.0–10.0)	7.0 (5.0–11.0)	0.05
Alcoholism	35 (17.8)	4 (21.1)	0.76	29 (16.7)	10 (23.8)	0.28
Antibiotics in previous 30 days	72 (36.5)	7 (36.8)	1.00	60 (34.5)	19 (45.2)	0.19
Chronic obstructive pulmonary disease	36 (18.3)	4 (21.1)	0.76	32 (18.4)	8 (19.0)	0.92
Decubitus ulcers	19 (9.6)	1 (5.3)	1.00	14 (8.0)	6 (14.3)	0.21
Diabetes	91 (46.7)	8 (42.1)	0.81	77 (44.5)	22 (53.7)	0.29
Heart failure	28 (14.2)	4 (21.1)	0.50	24 (13.8)	8 (19.0)	0.39
Hepatic dysfunction	22 (11.2)	5 (26.3)	0.07	17 (9.8)	10 (23.8)	0.01
History of cerebrovascular accident	17 (8.6)	1 (5.3)	1.00	14 (8.0)	4 (9.5)	0.76
History of healthcare exposure in preceding 180 days	91 (46.2)	12 (63.2)	0.16	72 (41.4)	31 (73.8)	<0.001
HIV	2 (1.0)	0 (0)	1.00	2 (1.8)	0 (0)	1.00
Hypertension	144 (73.5)	13 (68.4)	0.64	125 (72.3)	32 (76.2)	0.61
Immunosuppressant drug use	4 (2.0)	2 (10.5)	0.09	6 (3.4)	0 (0)	0.60
Malignancy or cancer	18 (9.1)	4 (21.1)	0.11	18 (10.3)	4 (9.5)	1.00
Renal dysfunction	42 (21.3)	7 (36.8)	0.12	37 (21.3)	12 (28.6)	0.31
Surgery in preceding 60 days	39 (19.8)	4 (21.1)	1.00	34 (19.5)	9 (21.4)	0.78
Residence in intensive care unit	20 (10.2)	5 (26.3)	0.04	22 (12.6)	3 (7.1)	0.43
Concomitant antibiotics	159 (80.7)	16 (84.2)	1.00	141 (81.0)	34 (81.0)	0.99
Cellulitis	148 (75.1)	16 (84.2)	0.58	131 (75.3)	33 (78.6)	0.66
Abscess	61 (31.0)	3 (15.8)	0.20	57 (32.8)	7 (16.7)	0.04
Chronic ulcer infection	50 (25.4)	4 (21.1)	0.79	41 (23.6)	13 (31.0)	0.32
Postoperative infection	27 (13.7)	2 (10.5)	1.00	21 (12.1)	8 (19.0)	0.23
Lymphadenitis	7 (3.6)	3 (15.8)	0.05	9 (5.2)	1 (2.4)	0.69
Location of Infection						
Lower extremity	142 (72.1)	13 (68.4)	0.82	123 (70.7)	32 (76.2)	0.35
Upper extremity	20 (10.2)	2 (10.5)		21 (12.1)	1 (2.4)	
Abdomen/torso	15 (7.6)	2 (10.5)		13 (7.5)	4 (9.5)	
Genitals	12 (6.1)	2 (10.5)		10 (5.7)	4 (9.5)	
Other/Unknown	8 (4.1)	0 (0)		7 (4.0)	1 (2.3)	
Microbiologic skin culture growth	126 (64.0)	12 (63.2)	0.95	114 (65.5)	24 (57.1)	0.31
Streptococcus spp.	37 (29.4)	1 (8.3)	0.18	33 (28.9)	5 (20.8)	0.62
Methicillin-susceptible *S. aureus*	30 (23.8)	3 (25.0)	1.00	28 (24.6)	5 (20.8)	0.80
Methicillin-resistant *S. aureus*	50 (39.7)	3 (25.0)	0.37	45 (39.8)	8 (33.3)	0.57
Polymicrobial culture	48 (38.1)	6 (50.0)	0.42	42 (36.8)	12 (50.0)	0.23
Enterococcus spp.	15 (11.9)	4 (33.3)	0.06	14 (12.3)	5 (20.8)	0.27
Gram-negative pathogen	10 (7.9)	1 (8.3)	1.00	8 (7.0)	3 (12.5)	0.41
Anaerobic pathogen	7 (5.6)	0 (0)	1.00	7 (6.1)	0 (0)	0.61
Concomitant bacteremia	14 (7.1)	2 (10.5)	0.64	13 (7.5)	3 (7.1)	1.00
Median duration of therapy (no. of days [IQR])	4 (3–7)	6 (5–11)	0.02	4 (3–7)	5 (3–7)	0.25

(Fig. 1). The greatest difference in 30-day readmissions between VA-AKI groups was among those with a non-SSSI-related readmission (Fig. 1). Bivariate comparisons of clinical characteristics between the 30-day readmission and non-30-day readmission groups and the VA-AKI and non-VA-AKI groups are shown in Table 1. In the multivari-

able analyses, VA-AKI was independently associated with 30-day hospital readmissions (adjusted odds ratio [aOR], 2.78; 95% confidence interval [CI], 1.00 to 7.80; $P = 0.05$) and non-SSSI-related 30-day readmissions (aOR, 4.66; 95% CI, 1.37 to 15.85; $P = 0.01$) but not SSSI-related 30-day readmissions (aOR, 1.12; 95% CI, 0.20 to 4.33; $P = 0.87$) after adjusting for hepatic dysfunction and health care exposure in the preceding 180 days.

Consistent with other studies that evaluated the outcomes of adult patients who survived a hospitalization complicated by AKI, irrespective of cause (12), patients who experienced VA-AKI had considerably higher rates of 30-day readmissions relative to those that did not experience VA-AKI. The higher incidence of 30-day admissions in the vancomycin-associated AKI group was driven by non-SSSI-related 30-days readmissions (Fig. 1). Closer inspection of the admitting diagnosis of patients with non-SSSI-related 30-day readmissions suggests that nearly all of the admissions were due to a cardiac or pulmonary condition. These are the most commonly involved systems in AKI-associated distal organ dysfunction or cross talk (8–11). Although the findings should be interpreted with caution, they clearly highlight the critical need to better understand the long-term consequences associated with VA-AKI, as the findings suggest that the sequela related to VA-AKI may persist even after renal function recovers.

Some things should be considered when interpreting these findings. First, the study population consisted of VA patients receiving vancomycin for the treatment of SSSIs, and the ability to generalize these findings to other populations may be finite. An advantage of studying VA patients is that the VA system is a closed health care system, and it is unlikely that any 30-day readmissions were missed. Second, we opted to use the most commonly employed definition of VA-AKI (14) versus other definitions used in the literature (15, 16). In a *post hoc* analysis, we examined the rates of readmissions among patients with a change in serum creatinine of $<$0.3, 0.3 to 0.49, and $\geq$0.5 mg/dl. Rates of readmissions were comparable among those with a creatinine change of $<$0.3 mg/dl (17.3%) and 0.3 to 0.49 mg/dl (16.7%). It was not until changes in creatinine exceeded 0.5 mg/dl that the occurrence of readmissions was significantly higher (42.1%). For those with a 2$\times$ to 3$\times$ increase in serum creatinine from baseline, the total number of patients was too small ($n = 7$) to make any inferences but was consistent with the 42.1% rates observed among those who met the definition of VA-AKI. While the terminology of VA-AKI was used for simplicity, the true causal mechanism of AKI in some instances may have been unrelated to vancomycin. It is unclear if this distinction would affect outcome.

In summary, the results suggest that hospitalized adult patients who experience VA-AKI may be at an elevated risk for non-SSSI-related 30-day readmissions. The admitting diagnoses of non-SSSI-related 30-day readmissions were consistent with the effects of AKI on remote organ dysfunction (8–11). Additional prospective studies elucidating the long-term consequences associated with vancomycin-associated AKI are warranted.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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Researchers interested in accessing the clinical data presented herewith are encouraged to submit a research proposal and publication plan.

Thomas P. Lodise and Nimish Patel led the development of the research question, study design, implementation of the study protocol, analysis and interpretation of the data, and drafting of the report. All authors were responsible for data interpretation and drafting of the report. All authors provided critical reviews and final approval of the manuscript. The approval of the manuscript and decision to submit the manuscript for publication were the responsibility of the coauthors led by Thomas P. Lodise.

REFERENCES

1. Magill SS, Edwards JR, Beldavs ZG, Dumyati G, Janelle SJ, Kainer MA, Lynfield R, Nadle J, Neuhauser MM, Ray SM, Richards K, Rodriguez R, Thompson DL, Fridkin SK, Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. 2014. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. JAMA 312:1438–1446. https://doi.org/10.1001/jama.2014.12923.
2. van Hal SJ, Paterson DL, Lodise TP. 2013. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother 57:734–744. https://doi.org/10.1128/AAC.01568-12.
3. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. 2007. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus pneumonia. Clin Ther 29:1107–1115. https://doi.org/10.1016/j.clinthera.2007.06.014.
4. Cano EL, Haque NZ, Welch VL, Cely CM, Peyrani P, Scerpella EG, Ford KD, Zervos MJ, Ramirez JA, Kett DH, Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia Study Group. 2012. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP database. Clin Ther 34:149–157. https://doi.org/10.1016/j.clinthera.2011.12.013.
5. Kullar R, Davis SL, Levine DP, Rybak MJ. 2011. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 52:975–981. https://doi.org/10.1093/cid/cir124.
6. Minejima E, Choi J, Beringer P, Lou M, Tse E, Wong-Beringer A. 2011. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrob Agents Chemother 55:3278–3283. https://doi.org/10.1128/AAC.00173-11.
7. Patel N, Huang D, Lodise T. 2018. Potential for cost saving with iclaprim owing to avoidance of vancomycin-associated acute kidney injury in hospitalized patients with acute bacterial skin and skin structure infections. Clin Drug Invest 38:935–943. https://doi.org/10.1007/s40261-018-0686-5.
8. Lee SA, Cozzi M, Bush EL, Rabb H. 2018. Distant organ dysfunction in acute kidney injury: a review. Am J Kidney Dis 72:846–856. https://doi.org/10.1053/j.ajkd.2018.03.028.
9. Doyle JF, Forni LG. 2016. Acute kidney injury: short-term and long-term effects. Crit Care 20:188. https://doi.org/10.1186/s13054-016-1353-y.
10. Kao CC, Yang WS, Fang JT, Liu KD, Wu VC. 2019. Remote organ failure in acute kidney injury. J Formos Med Assoc 118:859–866. https://doi.org/10.1016/j.jfma.2018.04.005.
11. Parr SK, Siew ED. 2016. Delayed consequences of acute kidney injury. Adv Chronic Kidney Dis 23:186–194. https://doi.org/10.1053/j.ackd.2016.01.014.
12. Silver SA, Harel Z, McArthur E, Nash DM, Acedillo R, Kitchlu A, Garg AX, Chertow GM, Bell CM, Wald R. 2017. 30-Day readmissions after an acute kidney injury hospitalization. Am J Med 130:163–172. https://doi.org/10.1016/j.amjmed.2016.09.016.
13. Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41. https://doi.org/10.1159/000180580.
14. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, Dalovisio JR, Levine DP. 2009. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49:325–327. https://doi.org/10.1086/600877.
15. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network. 2007. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11:R31. https://doi.org/10.1186/cc5713.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative Workgroup. 2004. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212. https://doi.org/10.1186/cc2872.