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# THE IMPACT OF VITAMIN C SUPPLEMENTATION ON VANCOMYCIN-INDUCED NEPHROTOXICITY

**Dr. Jonathan R. Anderson[1], Dr. Sarah A. Collins[2]**

**Article Info**

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**Abstract**

Vancomycin, a glycopeptide antibiotic, is a potent bactericidal agent that hinders bacterial cell wall synthesis. It is commonly prescribed for combating methicillin-resistant Staphylococcus aureus (MRSA) and other Gram-positive bacterial infections. Despite its effectiveness, the use of vancomycin can lead to nephrotoxicity, necessitating treatment discontinuation and resulting in adverse outcomes for patients. This review examines the clinical implications and management of vancomycin-induced nephrotoxicity, shedding light on its impact on patient morbidity and mortality. Understanding the risk factors, monitoring strategies, and potential interventions for vancomycin-associated nephrotoxicity is crucial in optimizing the therapeutic benefits while minimizing adverse effects. This comprehensive analysis provides valuable insights for healthcare professionals to enhance the safe and effective use of vancomycin in clinical practice.

## 1. Introduction

Vancomycin is a glycopeptide antibiotic that possesses bactericidal activity through inhibition of bacterial cell wall synthesis (Cooper & Williams, 1999). It is frequently administered for the treatment of methicillin-resistant *Staphylococcus aureus*(MRSA)and other Gram-positive organisms (Elyasi et al., 2012; Liu et al., 2011). While efficacious, vancomycin administration may be complicated by nephrotoxicity requiring discontinuation and consequent impact on patient morbidity and mortality (Wong-Beringer et al., 2011; Appenroth et al., 1997).

Nephrotoxicity has been associated with vancomycin particularly in patients receiving higher doses, prolonged treatment durations, and concomitant administration of other nephrotoxic agents (Elyasi et al., 2012; Hanrahan et al., 2014; Lodise et al., 2008; Pritchard et al., 2010).The exact mechanism of vancomycininduced nephrotoxicity (VIN) is uncertain, but various animal models have suggested renal tubular ischemia can manifest secondary to free radical formation and oxidative damage (Hazlewood et al., 2010; Nishino et al., 2002; Dieterich et al.,

[1] Texas Tech University Health Sciences Center School of Pharmacy, Abilene, TX, USA
[2] Mainland Medical Center, Texas City, TX, USA

2009).A recent meta-analysis by van Hal et al. collected 250 studies (15 met inclusion criteria) to assess the risk of VIN. The authors focused on the risk related tothe use of larger doses to achieve troughs of 15 to 20 mg/L. These higher doses were associated with higher odds of nephrotoxicity although most cases were reversible and only 3% required dialysis (van Hal et al., 2013).

VIN is defined and classified through various criteria used to assess acute kidney injury (AKI). Current guidelines by Rybak et al. define VIN as an increase of greater than 0.5 mg/dL (or at least 50% increase) in serum creatinine (SCr) from baseline in daily values or a decrease in calculated creatinine clearance of 50% from baseline in 48 hours, when all other causes are excluded (Rybak et al., 2009).In 2004 the Acute Dialysis Quality Initiative (ADQI) group published their consensus AKI diagnosis and classification system known as RIFLE (Bellomo et al., 2004). This system stratifies patients into three grade risks (Risk of renal dysfunction; Injury to the kidney; Failure of kidney function) and two clinical outcomes (Loss of kidney function; End-stage kidney disease) using glomerular filtration rate (GFR) criteria and urine output criteria. RIFLE class is determined based on the worst of either GFR criteria or urine output criteria. The time for AKI to occur includes SCr changes over 1-7 days, sustained for more than 24 hours.

The role of supplemental antioxidants to prevent nephrotoxicity is an area of interest with minimal conclusive data that has generated some controversy in recent years.Elyasi et al. analyzed previous studies that used agents for the prevention of VIN,concluding that erdosteine, vitamin E, vitamin C, N-acetylcysteine, caffeic acid phenethyl ester, and erythropoietin may be beneficial (Elyasi et al., 2012).

Vitamin C is a water-soluble antioxidant due to its ability to act as an electron donor and thus a reducing agent (Bellomo et al., 2004). Reduction reactions with damaging free radicals lead to the formation of less reactive molecules (also known as free radical scavenging) to lessen oxidative stress (Padayatty et al., 2003). A limited number of animal and *in vivo* studies suggest that high dose vitamin C may confer a renal-protective antioxidant effect by inhibiting renal glutathione depletion, lipid peroxidation, and glomerulosclerosis (Bielski et al., 1975; Ocak et al., 2007; Kadkhodaee et al., 2005). To date, no randomized controlled human studies have been performed to evaluate the clinical benefit of vitamin C in VIN.

The purpose of this study is to determine whether vitamin C is associated with a reduction in VIN compared to patients not receiving vitamin C. We postulate that vitamin C will mitigate the risk of AKI and therefore reduce hospital length of stay (LOS).

## 2. Methods

### *2.1. Study design*

An observational retrospective case-cohort study was conducted on patients admitted to Hendrick Medical Center receiving vancomycin therapy. Following Institutional Review Board approval, a list of patients meeting pre-defined inclusion and exclusion criteria was generated by Hendrick Medical Center's Information Technology Department.

### *2.2. Patients*

Hendrick Medical Center has utilized vitamin C with vancomycin therapy since 2008 based on the animal and invivo studies that showed renal protection effect of vitamin C (Padayatty et al., 2003; Bielski et al., 1975; Ocak et al., 2007).When a physician consulted pharmacy for vancomycindosing, a vitamin C regimen (500 mg PO BID for 2 doses) withvancomycin therapy was also considered by the physician.

Patients hospitalized between October 1, 2010 and August 31, 2013 were identified through a retrospective search of electronic medical records. Billing codes for vancomycin and vitamin C were used to identify patients of interest.Study subjects were eligible for inclusion if they were at least 18 years of age and had received at least 2

doses of vancomycin intravenously. Patients were excluded if they were receiving amphotericin B, antineoplastic agents, calcineurin inhibitors, or antifolates; had a previous history of renal calculi, dialysis or renal replacement therapy, and renal transplantation; were pregnant; or were prisoners/wards of the state.

Patients were classified as 'vitamin C' group if vitamin C was receivedwith vancomycin therapy and 'vancomycin only' group if vitamin C was not received.

*2.3. Data collection*

Data points were collected including subject demographics, LOS, ICU admissions, pertinent laboratory findings, comorbidities, infection types, vancomycin dose and trough levels, antibiotics received, and concomitant nephrotoxins received.

*2.4. Outcomes*

The primary outcome of this study was the incidence of AKI using the RIFLE criteria between the vitamin C group and vancomycin only group. The secondary outcome was LOS between groups.

**Figure 1:** RIFLE criteria

| **Category** | **GFR Criteria** | **Urine Output Criteria** |
|---|---|---|
| **Risk** | Increased SCr x1.5 or decreased GFR > 25% | UO < 0.5ml/kg/hr x 6 hours |
| **Injury** | Increased SCr x2 or decreased GFR > 50% | UO < 0.5ml/kg/hr x 12 hours |
| **Failure** | Increased SCr x3 or decreased GFR > 75% | UO < 0.3ml/kg/hr x 24 hours or anuria x 12 hours |
| **Loss** | Persistent ARF = complete loss of function > 4 weeks | |
| **End Stage** | End-stage renal disease (> 3 months) | |

RIFLE criteria (Bellomo et al, 2004); acute renal failure (ARF); urine output (UO); serum creatinine (SCr); glomerular filtration rate (GFR).

*2.5. Statistical Analysis*

Descriptive statistics, including n (%), mean and standard deviation, were implemented to characterize patient demographics and comorbidities. Student's t or one-way ANOVA was used to test for group differences in continuous outcome variables, while Chi Square or Fisher's Exact was used to test for group differences in categorical/dichotomous outcome variables. Phi correlation was used to assess the relationship of dichotomous independent variables with AKI.

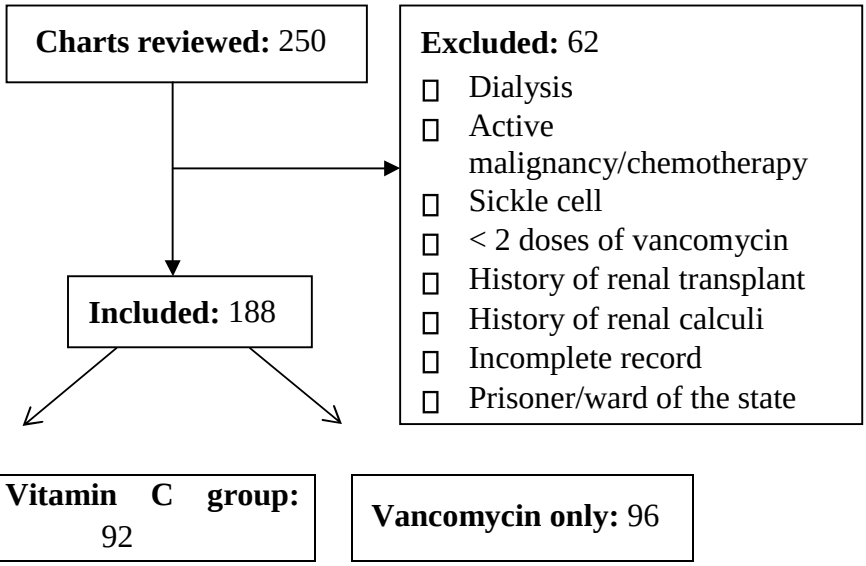
Multivariate logistic regression and multiple linear regression models were used to predict the relationship of AKI and LOS with vitamin C use, respectively, while controlling for covariates. Independent variables not significantly contributing to the regression models were removed in the interest of parsimony (while retaining the primary independent variable – vitamin C). A Bonferroni adjustment was implemented to control for Type I error inflation. The *a priori* level of significance was $\alpha = 0.05$.

Data analysis was performed using the SPSS® Statistical Software package version 20. Sample size calculations were performed using G*Power 3.1.3 software. Accounting for a model with up to 30 independent variables, moderate effect size ($f^2 = 0.15$), $\alpha = 0.05$, and power = 0.80, at least 187 study subjects were required.

## 3. Results

A total of 250 charts of patients that received vancomycin were screened, with 188 subjects meeting the inclusion criteria. Of these included subjects, 92 (48.9%) had received vitamin Cwith vancomycin, while 96 (51.1%) received only vancomycin (p=0.461). Figure 2 describes patient inclusion and exclusion information.

**Figure 2:** Flow chart of subject enrollment




The mean age was 60 ± 16.5 years, 57.4% of subjects were male, and 83.5% were Caucasian. Among all included study subjects, 48 were classified as experiencing AKI based on the RIFLE criteria.

Fewer instances of AKI were detected in the vitamin C group as compared to the vancomycin group; however this difference between groups was not statistically significant. The mean length of stay in the vitamin C group was 12.4 ± 14.33 vs. 8.4 ± 6.1 days in the vancomycin group (p=0.012). An admission to the ICU was required by 24 subjects (12.8%), with 7 in the vitamin C group, and 17 in the vancomycin group (p=0.49). Cardiovascular comorbidities were most prevalent in this study population; 45.7% had diabetes mellitus, 27.7% had hyperlipidemia, 26.3% had heart failure, and 18.6% had coronary artery disease. Group differences in renal characteristics including SCr, urine output, and pre-existing kidney disease were not found to be statistically significant. Regarding concomitant antibiotics and nephrotoxins, the two groups did not differ significantly on any variable after applying a Bonferroni adjustment to control for Type I error inflation. Baseline characteristics of study subjects are presented in Table 1 and 2.

**Table 1: Baseline characteristics of study subjects**

| Parameter | Total (n=188) | Vitamin C (n = 92) | Vancomycin only (n = 96) | p-value |
|---|---|---|---|---|
| Male (%) | 108 (57.4%) | 50 (54.3) | 58 (60.4) | .461 |
| Age (mean±SD; years) | 60 ± 16.5 | 61 ± 17.7 | 59 ± 15.3 | .378 |
| Weight (mean± SD; kg) | 92.4 ± 33.1 | 92.6 ± 31.6 | 92.3 ± 34.7 | .944 |
| Length of stay (days) | 10.4 ± 11.09 | 12.4 ± 14.33 7 | 8.4 ± 6.11 | .012 |
| ICU Admission (%) | 24 (12.8) | (7.6) | 17 (17.7) | .049 |
| Admit SCr (mean± SD; mg/dL) Baseline | 1.16 ± 0.803 | 1.12 ± 0.640 | 1.21 ± 0.935 | 0.445 |
| Ave SCr (mean± SD; mg/dL) | 1.06 ± 0.613 | 1.00 ± 0.355 | 1.11 ± 0.783 | 0.254 |
| Maximum SCr (mean± SD; mg/dL) Trough level (mean± SD; mg/dL) | 1.45 ± 1.313 | 1.48 ± 1.526 | 1.41 ± 1.076 | 0.701 |
| Urine Output (mean± SD; ml/kg/h) | 13.92 ± 5.19 | 14.37 ± 6.06 | 13.49 ± 4.15 | 0.259 |
| Ethnicity Caucasian | 1.047 ± 0.736 | 0.98 ± 0.670 | 1.11 ± 0.794 | 0.219 |
| Hispanic | | 72 (78.3) | 85 (88.5) | - |
| African-American | 157 (83.5) | 17 (18.5) | 8 (8.3) | - |
| Comorbid illness | 25 (13.3) | 3 (3.3) | 3 (3.1) | - |
| Arrhythmia | 6 (3.2) | | | |
| | | 11 (12.0) | 12 (12.5) | 1.00 |
| | 23 (12.2) | | | |
| Asthma | 14 (7.4) | 7 (7.6) | 7 (7.3) | 1.00 .779 |
| Cerebrovascular accident | 13 (6.9) | 7 (7.6) | 6 (6.3) | .711 |
| Coronary artery disease | 35 (18.6) | 16 (17.4) 8 | 19 (19.8) | .481 |
| Dementia | 20 (10.6) | (8.7) | 12 (12.5) | .057 |
| Diabetes mellitus | 86 (45.7) | 49 (53.3) | 37 (38.5) | .368 |
| Heart failure | 22 (11.7) 10 | 13 (14.1) 2 | 9 (9.4) | .101 |
| Hepatic disease | (5.3) | (2.2) | 8 (8.3) | .872 |
| Hyperlipidemia | 52 (27.7) | 26 (28.3) | 26 (27.1) | 1.00 1.00 |
| Malignancy | 26 (13.8) 14 | 13 (14.1) 7 | 13 (13.5) 7 | 1.00 |
| Myocardial infarction | (7.4) | (7.6) | (7.3) | .460 |
| Renal disease Sepsis | 21 (11.2) | 10 (10.9) | 11 (11.5) | |
| Concomitant antibiotics | 18 (9.6) | 7 (7.6) | 11 (11.5) | |
| Penicillins | 80 (42.6) | 38 (41.3) | 42 (43.8) | 0.769 |
| Cephalosporins | 107 (56.9) | 50 (54.3) | 57 (59.4) | 0.556 |
| Carbapenems | 35 (18.6) | 22 (23.9) | 13 (13.5) | 0.091 |
| Fluoroquinolones | 69 (36.7) | 28 (30.4) | 41 (42.7) | 0.096 |
| Aminoglycosides | 18 (9.6) | 9 (9.8) | 9 (9.4) | 1.000 |
| Tetracyclines | 7 (3.7) | 4 (4.3) | 3 (3.1) | 0.716 |
| Rifampin | 11 (5.9) | 6 (6.5) | 5 (5.2) | 0.764 |
| SMX/TMP | 13 (6.9) | 2 (2.2) | 11 (11.5) | 0.019 |
| Acyclovir | 4 (2.1) | 1 (1.1) | 3 (3.1) | 0.621 |
| Azoles | 21 (11.2) | 10 (10.9) | 11 (11.5) | 1.000 |
| Echinocandins | 4 (2.1) | 3 (3.3) | 1 (1.0) | 0.361 |

| | | | | |
|---|---|---|---|---|
| Metronidazole | 15 (8.0) | 8 (8.7) | 7 (7.3) | 0.792 |
| Macrolides/Lincosamide | 23 (12.2) | 12 (13.0) | 11 (11.5) | 0.825 |
| Infection site | | | | |
| Skin & soft tissue | 103 (55.1) | 54 (59.3) | 49 (51.0) | 0.304 |
| Diabetic foot | 12 (6.4) | 10 (11.0) | 2 (2.1) | 0.016 |
| Pneumonia | 36 (19.1) | 11 (12.0) | 25 (26.0) | 0.016 |
| Osteomyelitis | 17 (9.0) | 13 (14.1) | 4 (4.2) | 0.022 |
| Intra-abdominal | 7 (3.7) | 3 (3.3) | 4 (4.2) | 1.000 |
| Urinary tract | 11 (5.9) | 2 2.2) | 9 (9.4) | 0.058 |
| Central nervous | 6 (3.2) | 1 (1.1) | 5 (5.2) | 0.212 |
| Concomitant nephrotoxins | | | | |
| NSAID | 76 (40.4) | 41 (44.6) | 35 (36.5) | 0.299 |
| Allopurinol | 5 (2.7) | 2 (2.2) | 3 (3.2) | 1.000 |
| Diuretics | 81 (43.1) | 38 (41.3) | 43 (44.8) | 0.660 |
| ACE inhibitors/ARB | 81 (43.1) | 40 (43.5) | 41 (42.7) | 1.000 |
| Radiocontrast | 38 (20.2) | 25 (27.2) | 13 (13.5) | 0.029 |

**Table 2: Incidence of acute kidney injury**

| Parameter | (n=188) | Vitamin C (n = 92) | Vancomycin only (n = 96) | p-value |
|---|---|---|---|---|
| AKI based on RIFLE criteria [N (%)] | 48 (25.5%) | 20 (21.7) | 28 (29.2) | 0.48 |
| Risk | 13 (27.1) | 3 (15.0) | 10 (35.7) | 0.188 |
| Injury | 15 (31.3) | 6 (30.0) | 9 (32.1) | 1.00 |
| Failure | 19 (39.6) | 11 (55.0) | 8 (28.6) | 0.080 |
| Loss | 1 (2.1) | 0 (0) | 1 (3.6) | 1.00 |
| End-stage | 0 (0) | 0 (0) | 0 (0) | - |

*3.1 Bivariate correlations of significant independent variables with acute kidney injury*

The effects of subject characteristics, medications, and comorbidities on AKI are presented in Table 3.Using Phi correlation and point-biserial correlation to assess the relationship betweenindependent variables and AKI, significant association was found with LOS, ICU admission, intra-abdominal infections,history of hypertension, history of coronary artery disease, sepsis,vancomycin dose & trough levels,carbapenem use, linezolid use, and diuretic use. Vitamin C use was not found to be significantly associated with AKI (p=0.245).

**Table 3: Bivariate correlations of statistically significant independent variables with acute kidney injury**

| Variable | p-value | Correlation coefficient (r) |
|---|---|---|
| Vitamin C | 0.245 | -0.085 |
| Length of stay | < 0.001 | 0.296 0.288 0.166 0.148 |
| ICU admission | < 0.001 | 0.207 |
| Vancomycin trough | 0.027 0.042 | 0.224 |
| Vancomycin dose | 0.004 0.002 | 0.230 0.190 0.171 0.228 |
| Intra-abdominal infection | 0.002 0.009 | 0.159 |
| Sepsis | 0.019 0.002 | |
| Diuretic use | 0.030 | |
| Carbapenem use | | |
| Linezolid use | | |
| Hypertension history | | |
| Coronary artery disease history | | |

*3.2 Logistic regression analysis of significant independent variables with acute kidney injury*

A multivariate logistic regression model was developed to predict the occurrence of AKI based on multiple independent variables, while controlling for all salient covariates. The Omnibus Tests of Model Coefficients and

the Hosmer&Lemeshow test were performed to indicate goodness of fit. The Nagelkerke $R^2$=0.371, suggesting that the model explained 37.1% of the variance. The results of this model and tests are presented in Table 4. Notably, the adjusted odds ratio (OR) for vitamin C was 0.377; (95% [CI], 0.15 to 0.90; p=0.029). Although bivariate analyses did not find that vitamin C was associated with AKI, comprehensive multivariate analyses controlling for covariates indicated that an association. For all other independent variables in the model, the adjusted ORs were great than 1.

**Table 4: Logistic regression model of statistically significant independent variables with acute kidney injury**

| Variable | Odds Ratio (adjusted) | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| Vitamin C | 0.377 1.081 | 0.029 | 0.15 1.02 1.69 | 0.90 |
| Length of stay | 6.724 4.290 | 0.005 | 1.39 1.76 | 1.14 |
| ICU admission | 9.688 | 0.007 | 3.29 | 26.27 13.21 |
| Skin & soft tissue infection | 41.647 | 0.011 | 1.76 | 53.26 |
| Diabetic foot infection | 4.591 | 0.009 | 1.04 | 525.78 |
| Intra-abdominal infection | 2.667 | 0.004 | | 11.93 |
| Hypertension history | | 0.002 | | 6.79 |
| Coronary artery disease history | | 0.400 | | |

Omnibus Tests of Model Coefficients: statistically significant, indicating goodness of fit. ($\chi^2$= 54.023, df = 8, p < .001) Hosmer and Lemeshow test: nonsignificant, indicating goodness of fit. (p = .280)Nagelkerke $R^2$= 0.371

*3.3 Bivariate correlations ofsignificant independent variables with length of stay*

The effects of subject characteristics, medications, and comorbidities on LOS are presented in Table 5. Using Pearson correlation to assess the relationship between independent variables and LOS, significant association was found with ICU admission, skin and soft tissue infections (SSTI), osteomyelitis, vancomycin dose & trough levels, number of days on vancomycin, history of myocardial infarction, sepsis, carbapenem use, fluoroquinolone use, azole antifungal use, metronidazole use, daptomycin use, and diuretic use. Vitamin C use was also found to be significantly associated with LOS (p=0.012).

**Table 5: Bivariate correlations of statistically significant independent variables with length of stay**

| Variable | p-value | Correlation coefficient (r) |
|---|---|---|
| Vitamin C | 0.012 | 0.184 0.332 |
| ICU admission | < 0.001 | 0.209 |
| Vancomycin trough | 0.005 | - 0.174 |
| Vancomycin dose | 0.017 | 0.572 |
| Days on vancomycin | < 0.001 | - 0.157 |
| Skin & Soft Tissue infection | 0.032 | 0.282 0.158 0.247 0.183 |
| Osteomyelitis | < 0.001 | 0.325 0.199 0.253 0.361 |
| Sepsis | 0.030 0.001 | 0.215 |
| Diuretic use | 0.012 | |
| Daptomycin use | < 0.001 | |
| Carbapenem use | 0.006 | |
| Fluoroquinolone use | < 0.001 | |
| Metronidazole use | < 0.001 | |
| Azole antifungal use | 0.003 | |
| Myocardial infarction history | | |

*3.4 Linear regression analysis of significant independent variables with length of stay*

A multiple linear regression model was used to predict LOS based upon statistically significant independent variables, while controlling for all salient covariates. The adjusted $R^2$=0.622, suggesting that 62.2% of the variance was explained by the model. This model also achieved goodness of fit; F = 20.097, df = (16, 170), p < .001.The results of this model and test are presented in Table 6. This model indicated that any relative impact of vitamin C on LOS was not statistically significant: 2.114; (95% [CI], -0.008 to 4.237; p=0.051). Although bivariate analyses showed that vitamin C was associated with LOS, comprehensive multivariate analyses controlling for covariates indicated that vitamin C was not. Of note, all other independent variablessignificantly impacted LOS.

**Table 6: Linear regression model of statistically significant independent variables with length of stay**

| Variable | Impact on LOS (days) | p-value | 95% Confidence Interval Lower bound | Upper bound |
|---|---|---|---|---|
| Vitamin C | 2.114 6.242 | 0.051 | - 0.008 | 4.23 9.57 |
| ICU admission | 1.026 | < | 2.91 | 1.25 |
| Days on vancomycin | - 5.485 | 0.001 | 0.80 | - 2.40 |
| Pneumonia | 7.316 7.396 | < | - 8.56 | 10.87 |
| Osteomyelitis | 3.720 3.442 | 0.001 | 3.75 3.05 | 11.73 |
| Daptomycin use | 5.346 3.547 | 0.001 | 1.60 1.35 | 5.83 5.52 |
| Penicillin use | 6.837 7.185 | < | 2.61 1.23 | 8.07 |
| Cephalosporin use | 6.639 4.338 | 0.001 | 3.00 0.26 | 5.86 |
| Carbapenem use | 6.590 | 0.001 | 0.31 1.04 | 10.66 |
| Fluoroquinolone use | | 0.001 | 2.61 | 14.10 |
| Metronidazole use | | 0.001 | | 12.96 |
| Acyclovir use | | < | | 7.62 |
| Allopurinol use | | 0.001 | | 10.57 |
| Heart failure history | | 0.003 | | |
| Myocardial infarction history | | 0.001 | | |
| | | 0.042 | | |
| | | 0.040 | | |
| | | 0.010 | | |
| | | 0.001 | | |

F = 20.097, df = (16, 170), p < .001, indicating the model achieves goodness of fit. Adjusted $R^2$= 0.622

## 4. Discussion

In this retrospective study conducted at a 500-bed community hospital in west Texas, the use of vitamin C was found to be associated with AKI but not LOS.

For the primary outcome, within the population represented by the sample, vitamin C was associated with a reduced likelihood of AKI.Fewer instances of AKI were detected in the vitamin C group as compared to the vancomycin group, 21.7% vs. 29.2%, (p=0.248).Using correlational analyses, significant association between vitamin C and AKI was not detected. However, multivariate logistic regression analysis indicated that vitamin C was associated with reduced odds of AKI by 62.3%.

For the secondary outcome, LOS was found to be longer in the vitamin C plus vancomycin group as compared to the vancomycin only group (12.4 ± 14.33 vs. 8.4 ± 6.11 days; p=0.012) and, using correlational analyses, vitamin C use was also found to be significantly associated with LOS (p=0.012);whereas multiple linear regression analyses indicated that any relative impact of vitamin C on LOS was not statistically significant: 2.114; (95% [CI], -0.008 to 4.237; p=0.051).

This may suggest that vitamin C does not significantly increase length of stay,while other patient comorbid conditions likely affected the LOS.

Current literature points to a potentialrenal-protective benefit associated with vitamin C.Ocak et al. tested the use of vitamin E, vitamin C (concentration of 200 mg/dl), n-acetylcysteine (NAC) and caffeic acid phenethyl ester (CAPE) in a rat model to prevent VIN. In this study, vitamin E was found to be most effective for preventing renal tubular damage, followed by vitamin C, NAC, and CAPE. Blood urea nitrogen (BUN), renal malondialdehyde, and nitric oxide levels were used to assess renal dysfunction. BUN changes were statistically significant within the vitamin E and C groups ($p < 0.05$). However, renal malondialdehyde and nitric oxide levels were significantly suppressed by all of the agents used in the study ($p < 0.05$) (Ocak et al., 2007).

A 2005 study conducted by Kadkhodaee and colleagues analyzed the benefit of vitamin C in a rat model by using biomarkers such as urinary lactate dehydrogenase (LDH), N-acetyle-β-D-glucosaminidase (NAG) and alkaline phosphatase (ALP) activities, inulin clearance (glomerular filtration rate, GFR) and renal tissue glutathione (GSH) content. Following the administration of vitamin C (100 mg), urinary enzyme activity increase was inhibited; however, GSH and GFR did not improve significantly. Investigators also administered vitamin E, and concomitant use of both showed significantassociation with GFR and GSH preservation (Kadkhodaee et al., 2005).

In another study by Antuneset al.,investigators evaluated the utility of vitamin C for the prevention of cisplatin-induced nephrotoxicity in adult rats. Vitamin C was provided in three different doses (50 mg/kg, 100 mg/kg, 200 mg/kg). The renal toxicity was assessed by renal glutathione levels, SCr levels and creatinine clearance. Glomerular damage caused by cisplatin was attenuated in a dose dependent manner - larger doses of vitamin C appeared more effective. Creatinine clearance, glutathione levels and SCrlevels were recovered significantly ($p < 0.05$) 7 days post cisplatin administration (Antunes et al., 2000).

Recently, Moreira et al. observed the effect of vitamin C (1.0 g/kg/day)on gentamicin-induced acute renal failure in rats. They used serum urea and creatinine, serum and renal tissue malondialdehyde, blood superoxide anion and hydrogen peroxide as markers of oxidative damage. All of these markers were increased in the group receiving gentamicin when compared to the control and vitamin C groups. The vitamin C and gentamicin group showed a decrease in these markers ($p < 0.05$). In the group receiving gentamicin nitric oxide was increased in serum and decreased in urine, when vitamin C was administered in combination with gentamicin serum nitric oxide decreased ($p < 0.0001$). Damage of proximal tubules was evident in the gentamicin group, whereas only mild lesions were seen in the gentamicin and vitamin C group.

The authors concluded that vitamin C increased urinary nitric oxide and decreased the production of reactive oxygen species,thus preventingnephronal damage (Moreira et al., 2014).

A major limitation of this study was the utilization of retrospective design conducted at a single site. Thus, these findings should not be interpreted as establishing causality, but rather be used for further hypothesis generating.Also, the reliance upon nurse-driven charting and written physician progress notes may have limited the completeness of patient data and introduced recall bias. Additionally, the predictive capacity of the RIFLE criteria may be inadequate. The RIFLE criteria may be hampered by missing SCr or GFR data, diuretic use, and smaller changes in SCr that may not qualify under class “Risk”.Studies have shown thatabsolute increasesas little as 0.3 mg/dl are associated with poor outcomes (Chertow et al., 2005; Finlay et al., 2013).Lastly, it is unclear what dose of vitamin C provides the greatest benefit. Previous studies performed in rodent models varied greatly in dosing strategy and administered significantly smaller doses than those received by subjects within this study.

This study is strengthened by the fact that outcomes were statistically adjusted to control for the potential impact of covariates such as severity of illness, multiple comorbidities and nephrotoxic agents. Additionally, sufficient numbers of patients were included to achieve the pre-specified power of 80%. This study is further strengthened by the consistent dosing and administration of vitamin C 500 mg by mouth twice daily. Likewise, pharmacist-managed vancomycin dosing minimized key confounders such as therapeutic failure and associated adverse events.

## 5. Conclusion

In conclusion, this study found that vitamin C was associated with a 63%reduction in AKI, but did not impact LOS.Thisstudy is the first to examine the use of Vitamin C for the prevention of VIN in humans, whereas previous studies were conducted only in rat models.Our study supports the findingsof the animal datathat vitamin C supplementation may confer a renal-protective benefit and mitigate hospital complications.This study may expand upon currently limited data and contribute to hypothesis-generating for future randomized clinical trials.

## Rererences

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