

# Comparative Incidence of Nephrotoxicity by Age Group among Adult Patients Receiving Vancomycin

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## ABSTRACT

**Introduction:** Little is known regarding age-related risk of nephrotoxicity during vancomycin therapy after the publication of the 2009 vancomycin consensus guidelines for therapeutic drug monitoring. We sought to evaluate incidence and risk factors for acute kidney injury in three age groups.

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**Methods:** Matched cohort study of patients receiving vancomycin, grouped by age: young adults (18–64 years), older adults (65–79 years) and very elderly ( $\geq 80$  years), matched on previously published risk factors for nephrotoxicity. Outcomes included traditional vancomycin nephrotoxicity and Acute Kidney Injury Network-modified definition of nephrotoxicity.

**Results:** The incidence of acute kidney injury was 34.1% vs. 34.1% vs. 31.8% in the young, older adults and very elderly groups, respectively ( $p = 0.97$ ). In the logistic regression model, after adjusting for baseline risk factors, age was not a significant predictor of acute kidney injury. Lower respiratory tract infection (adjusted odds ratio [aOR] 5.18; 95% confidence interval [CI] 2.15–12.41) and duration of treatment (aOR 1.12; 95% CI 1.03–1.22) were found to be independently associated with outcome.

**Conclusion:** No differences in risk of acute kidney injury were identified between young, older, and very elderly adults when adjusting for other risk factors. Further research is required to identify strategies to optimize the safety of vancomycin in the aging population.

**Keywords:** Acute kidney injury; Aged; Drug toxicity; Elderly; Infectious diseases; Nephrotoxicity; Vancomycin

## INTRODUCTION

Vancomycin has long been the workhorse agent for management of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA); however, its clinical use is limited by nephrotoxicity [1–10]. While older data suggested that nephrotoxicity was initially associated with impurities in original formulations [1, 11], newer data suggest that nephrotoxicity is associated with risk factors, including patient-specific risk factors [8, 9], concurrent nephrotoxins [5–7, 10] and greater vancomycin exposures [2, 3]. Risk factor identification has greatly improved the ability of clinicians to determine which patients are at high risk for nephrotoxicity.

Despite improvements in the literature and practice, there are still limited data on renal safety of vancomycin in the very elderly (age  $\geq 80$  years old). In 2002, the United Nations deemed the very elderly to be the fastest growing age group worldwide [12]. As of 2010, in the United States, when a person survives up to age 80, they are expected to live an additional 9.1 years [13]. This increased time at risk for infectious diseases, coupled with an increased prevalence of MRSA infections [14], establishes a great need for information on the safety of vancomycin in these patients.

Previous investigations have provided valuable insight into age-related differences in risk of nephrotoxicity with vancomycin use. Twenty years ago, Vance-Bryan et al. [7] conducted a retrospective cohort study examining the comparative incidence of nephrotoxicity in the elderly (age  $\geq 60$  years)

and young (age  $< 60$  years). This study observed an increase in nephrotoxicity in the elderly population; however, this difference was thought to be due to an unequal distribution of other risk factors, like use of loop diuretics [7]. Since then, routine targets for vancomycin serum trough concentrations have changed, with recommendations of troughs greater than 10 mg/L for all patients, and 15–20 mg/L for specific indications [15]. The most recent data observing vancomycin nephrotoxicity have linked elevated serum trough concentrations and nephrotoxicity [3, 5, 9]; some of the studies have adjusted for age, however, none have been designed a priori to compare nephrotoxicity across age groups. The present study was conducted to estimate the relative risk of nephrotoxicity in very elderly adults receiving vancomycin as compared to older (65–79 years) and younger adults ( $< 65$  years) while controlling for differences in baseline risk of nephrotoxicity.

## MATERIALS AND METHODS

### Study Design

This was an institutional review board-approved, retrospective, matched cohort study at an urban, tertiary care teaching hospital serving a wide variety of medical and surgical specialties. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was waived by the institutional review board.

Patients receiving intravenous (IV) vancomycin between January 2011 and April 2013 were screened. Patients included were

aged at least 18 years, received at least four consecutive vancomycin doses, and had at least one recorded vancomycin serum trough concentration during the course of therapy. Patients were excluded if they had concurrent acute kidney injury prior to initiation of vancomycin (defined as an increase in serum creatinine of 0.3 mg/dL or 50% within 48 h prior to starting vancomycin, or if urine output was <0.5 mL/kg/h for at least 6 h immediately before the initiation of vancomycin), were pregnant, or had an absolute neutrophil count <1,000 cells/mm<sup>3</sup>.

Patients were categorized by age as young (18–64 years), older adults (65–79 years) and very elderly ( $\geq 80$  years). Consecutive very elderly patients were matched 1:1:1 with consecutive young and older adult patients on the basis of four classes of risk factors for nephrotoxicity: (1) history of acute kidney injury [8] or pre-existing chronic renal disease (as noted by baseline serum creatinine  $\geq 1.30$  mg/dL), (2) weight  $\geq 110$  kg or receipt of high-dose IV vancomycin (at least 4 g per day) [2], (3) concurrent receipt of nephrotoxins (e.g., acyclovir, IV aminoglycosides, IV amphotericin B, IV contrast dye, loop diuretics, IV colistin) [1, 6, 16] with IV vancomycin, and (4) concurrent receipt of IV vasopressors (norepinephrine, phenylephrine, or dopamine) with IV vancomycin. Vancomycin was dosed as an intermittent infusion by clinical pharmacists in accordance with the 2009 consensus guidelines for vancomycin therapeutic drug monitoring [15]. The primary outcome of interest was nephrotoxicity, defined as an abrupt (within 48 h) increase in serum creatinine of 0.5 mg/dL or 50% above baseline for at least two consecutive measurements [15]. Secondary outcomes included Acute Kidney Injury Network (AKIN)-modified definition of nephrotoxicity [8], defined as an increase in

serum creatinine of 0.3 mg/dL, a decrease in creatinine clearance of at least 50% or a decrease in urine output to <0.5 mL/kg/h for at least 6 h.

### Data Analysis

Descriptive statistics were used to characterize the cohort with respect to patient demographics, treatment characteristics and outcomes. Categorical data were described as proportions, and continuous data were described as means and standard deviations or medians and interquartile ranges, as appropriate. Outcomes and patient characteristics were compared between age groups.

Odds ratios were calculated for odds of nephrotoxicity and acute kidney injury for each age group with the young group as a reference category. Categorical data were analyzed using Chi-square test. Continuous parametric data were analyzed using one-way analysis of variance. Continuous non-parametric data were analyzed via one-way Kruskal–Wallis analysis of variance test, where appropriate. Lastly, a multivariable logistic regression model was constructed to determine the association between the age group and nephrotoxicity and acute kidney injury. Age was entered into the model and any variables found to have an association with the outcome of interest ( $p < 0.20$ ) or that had clinical rationale were considered for the multivariable logistic regression model using backward-stepwise regression. All analyses were conducted using SPSS<sup>®</sup> software, version 21.0 (SPSS Inc., Chicago, IL, USA).

Sample size assumption was based on the risk of nephrotoxicity in previously published studies [2], with a 7-day median duration of therapy, maximum risk (approximately 35%) in the very elderly and minimal risk (approximately 10%) in the young group. In

order to detect a difference at a 0.05 level of significance and with 80% power, approximately 40 patients were needed in each age group.

## RESULTS

Data were obtained for 132 patients meeting inclusion criteria. There were 44 patients in each stratum. Baseline characteristics (Table 1) were similar between groups, with limited exceptions other than age-related differences. The most common indications for vancomycin treatment were lower respiratory tract, bloodstream and skin and soft tissue infections. All patients had vancomycin trough concentrations obtained at steady state: in the respective young, older adults and very elderly groups, 75.0%, 77.3% and 77.3% of patients had an initial concentration greater than 10 mg/L, and 47.7%, 45.5% and 31.8% of patients had a 15 mg/L or greater concentration. The two most common baseline risk factors for nephrotoxicity were history of acute kidney injury or chronic kidney disease (36.4%) and concurrent receipt of nephrotoxins (36.4%). Duration of treatment was significantly longer in the elderly group vs. all other groups (9 vs. 7 days, respectively;  $p = 0.02$ ).

There were seven episodes of nephrotoxicity and 44 episodes of acute kidney injury within the cohort. The incidence of nephrotoxicity was 2.3%, 9.1% and 4.5% in the young, older adult and very elderly groups, respectively ( $p = 0.35$ , Fig. 1). The incidence of acute kidney injury was 34.1%, 34.1% and 31.8% in the young, older adults and very elderly groups, respectively ( $p = 0.97$ , Fig. 1). Relevant predictors for acute kidney injury, including all variables with  $p < 0.2$  in bivariate comparison, are listed in

Table 2. Since there were only seven episodes of nephrotoxicity, only acute kidney injury was explored in the multivariable analysis.

In the logistic regression model, age was entered into the model using the young group as the reference. Based on the pre-specified criteria for model entry and removal, age, lower respiratory tract infection, length of therapy and presence of at least two different risk factors at baseline were included in the final model. Age was not identified as a significant predictor. Adjusting for the presence of more than one baseline risk factor, both lower respiratory tract infection and longer duration of therapy were significant predictors for acute kidney injury.

## DISCUSSION

In the era of the 2009 consensus vancomycin guidelines, no independent association between acute kidney injury and advanced age was found in this matched cohort. These findings are similar to work predating these consensus recommendations [7]. Therefore, clinicians should not routinely use age alone to assess the risk of nephrotoxicity in patients receiving vancomycin. Factors that were found to be associated with acute kidney injury in our study included lower respiratory tract infection and longer duration of therapy, which are also consistent with more recent observational studies [3, 9]. Importantly, the multivariable analysis of this study was based on the secondary endpoint of AKIN-defined nephrotoxicity. The AKIN method of identifying nephrotoxicity has been shown to be more sensitive than the traditional definition of nephrotoxicity [15], and also explains the higher incidence of acute kidney injury identified in this cohort.

**Table 1** Baseline characteristics

Variable	Young ( <i>n</i> = 44)	Older adults ( <i>n</i> = 44)	Very elderly ( <i>n</i> = 44)	<i>p</i>
Age (years)	52 (41–59)	70 (66–75)	87 (82–90)	<0.01
Male sex	21 (48)	19 (43)	20 (46)	0.91
Baseline SCr (mg/dL)	0.86 (0.67–1.2)	1.00 (0.71–1.24)	1.07 (0.96–1.36)	0.01
CrCl (mL/min)	73 (54–92)	45 (37–60)	34 (26–45)	<0.01
Charlson score	1 (0–3)	2 (1–3)	2 (1–3)	0.11
Race				
Caucasian	18 (40.9)	11 (25.0)	19 (43.2)	0.11
African American	21 (47.7)	21 (47.7)	22 (50.0)	
Hispanic	1 (2.3)	0 (0.0)	0 (0.0)	
Asian	1 (2.3)	4 (9.1)	0 (0.0)	
Other	3 (6.8)	8 (18.2)	3 (6.8)	
Infection site <sup>a</sup>				
Abdominal	1 (2.3)	3 (6.8)	0 (0.0)	0.16
Blood	11 (25.0)	9 (20.5)	13 (29.5)	0.61
Bone	3 (6.8)	1 (2.3)	1 (2.3)	0.44
Central nervous system	3 (6.8)	0 (0.0)	4 (9.1)	0.14
Genitourinary	2 (4.5)	7 (15.9)	8 (18.2)	0.12
Joint	0 (0)	0 (0)	1 (2.3)	0.36
Lower respiratory tract	13 (29.5)	19 (43.2)	17 (38.6)	0.40
Skin and soft tissue	9 (20.5)	5 (11.4)	5 (11.4)	0.37
Wound	2 (4.5)	0 (0)	0 (0)	0.13
Other	3 (6.8)	2 (4.5)	1 (2.3)	0.59
Goal vancomycin trough 15–20 mg/L	31 (70.5)	30 (68.2)	34 (77.3)	0.61
Length of treatment (days)	7 (5–9)	9 (6–12)	7 (5–10)	0.05
Risk factors for nephrotoxicity				
History of AKI or chronic kidney disease	16 (36.4)	16 (36.4)	16 (36.4)	1.00
High-dose vancomycin <sup>b</sup> or weight ≥110 kg	1 (2.3)	1 (2.3)	1 (2.3)	1.00
Vasopressors	2 (4.5)	2 (4.5)	2 (4.5)	1.00
Nephrotoxins <sup>c</sup>	16 (36.4)	16 (36.4)	1 (36.4)	1.00

Data are median (interquartile range) or *n* (%)

AKI acute kidney injury, CrCl creatinine clearance, SCr serum creatinine

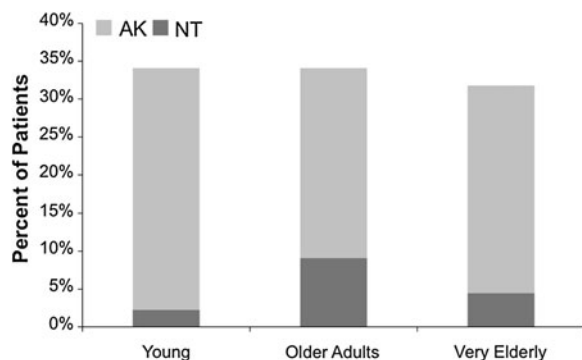
<sup>a</sup> Infection sites are not mutually exclusive

<sup>b</sup> At least 4 g of vancomycin per day

<sup>c</sup> Acyclovir, IV aminoglycosides, IV amphotericin B, IV contrast dye, loop diuretics, IV colistin

There are several potential explanations for the finding that lower respiratory tract infection was associated with nephrotoxicity. Recent guidelines recommend that due to poor lung penetration of vancomycin [17], a target trough of 15–20 mg/L is utilized for these infections

[15, 18, 19]. This target trough has also been associated with increased incidence of nephrotoxicity [3, 5, 6, 9]. In the present study, targeting a trough concentration of 15–20 mg/L was associated with nephrotoxicity in bivariate analysis; because of



**Fig. 1** Incidence of nephrotoxicity in each age group. *AKI* acute kidney injury, *NT* nephrotoxicity

covariance with lower respiratory tract infections, the stronger bivariate predictor was used in the multivariate model. In addition, the associated pathology of sepsis in patients with lower respiratory tract infections may increase

the risk of acute kidney injury. Sepsis has been shown in experimental models to increase the risk of acute kidney injury [20]; however, septic shock, as evidenced by use of vasopressors, was not common in this cohort.

This study is not without limitations. As with any retrospective study, causality cannot be proven, and data are subject to observer biases at the time of documentation. There is also the possibility that measured and unmeasured confounders influenced outcome. The matched cohort design with multivariable analysis may have reduced this effect. This is the first matched study to specifically examine the relationship between age and acute kidney injury during vancomycin therapy. These data must be considered carefully. Although a

**Table 2** Bivariate and multivariate associations with acute kidney injury

Variable	OR	95% CI	<i>p</i>	aOR	95% CI	<i>p</i>
Age group						
Young (reference)	1.00	N/A	N/A	1.00	N/A	N/A
Older adults	1.00	0.41–2.42	1.00	0.69	0.25–1.92	0.48
Very elderly	0.90	0.37–2.20	0.82	0.78	0.28–2.26	0.80
CrCl (mL/min)	0.98	0.96–1.00	0.05	–	–	–
Charlson score	1.30	1.05–1.61	0.02	–	–	–
Infection site <sup>a</sup>						
Blood	0.36	0.14–0.94	0.03	–	–	–
Genitourinary	0.38	0.11–1.43	0.14	–	–	–
Lower respiratory tract	4.08	1.90–8.78	<0.01	5.18	2.15–12.41	<0.01
Goal vancomycin trough 15–20 mg/L	2.21	0.91–5.36	0.07	–	–	–
Length of treatment (days)	1.08	1.00–1.16	0.04	1.12	1.03–1.22	<0.01
Risk factors for nephrotoxicity						
Vasopressors	4.30	0.76–24.46	0.10	–	–	–
Nephrotoxins	2.06	0.98–4.35	0.06	–	–	–
≥2 risk factors at baseline	7.00	2.08–23.55	<0.01	6.94	1.81–26.66	<0.01

aOR adjusted odds ratio, CI confidence interval, CrCl creatinine clearance, OR odds ratio

<sup>a</sup> Infection sites are not mutually exclusive. Data are median (interquartile range) or *n* (%)



matched cohort provides considerable evidence that age alone is not a significant risk factor for acute kidney injury during vancomycin therapy, extrapolation of kidney injury incidence within the general population is more difficult. These data provide an additional rationale for exercising caution when using vancomycin in patients requiring longer duration of therapy or with pre-existing risk factors, regardless of age.

## CONCLUSION

In this matched cohort study, there was no difference detected in risk of nephrotoxicity or acute kidney injury between young, older, and very elderly adults receiving vancomycin in an acute care inpatient facility. Further research is required to identify strategies to optimize the safety of vancomycin in the aging population.

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Dr. Susan L. Davis is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

**Conflict of interest.** Joseph J. Carreno, Anthony Jaworski and Rachel M. Kenney declare no conflict of interest.

Susan L. Davis has served as a paid consultant with Forest Inc., Durata, and Premier Inc.

**Compliance with ethics guidelines.** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was waived by the institutional review board.

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