

Assessing the Epidemiology of Nephrotoxicity and the Role of Urinary Kidney Injury Molecule 1 as a Biomarker of Renal Function in Hematologic-Oncologic Patients Under Vancomycin Treatment in Shiraz, Iran

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Received 2016 July 16; Revised 2016 August 18; Accepted 2016 September 05.

Abstract

Background: Nephrotoxicity is a common adverse effect of vancomycin. However, some aspects of vancomycin nephrotoxicity have not been studied well in the Iranian population. Serum creatinine as a classic marker of renal function has several limitations in clinical practice.

Objectives: To determine the incidence, time onset, and possible associated factors of vancomycin nephrotoxicity, and compare the patterns and the accuracy of urine kidney injury molecule 1 (KIM-1) with that of serum and urine creatinine during vancomycin treatment.

Methods: A longitudinal study was performed during 9 months from August, 2015 to April, 2016 at three hematology-oncology wards of the Namazi Hospital in Shiraz, Iran. Patients > 18 years with no documented history of acute kidney injury or chronic kidney disease scheduled to receive vancomycin for at least 1 week were recruited. Required demographic and clinical data of patients were gathered. Serum, as well as urine creatinine and urine KIM-1, were determined at days 0, 3, 5, 7, 10, and 14 of vancomycin treatment.

Results: Thirteen out of the 52 recruited patients (25%) developed nephrotoxicity, with a mean \pm standard deviation onset of 11.46 ± 7.56 days. Furosemide co-administration (odds ratio = 0.126, 95% confidence interval = 0.023-0.694, $P = 0.017$) was significantly associated with vancomycin nephrotoxicity. Vancomycin nephrotoxicity resolved spontaneously in about two-fifths (38.46%) of the affected individuals. Mortality ($P = 1$) and duration of hospitalization ($P = 0.175$) were comparable between patients with and without nephrotoxicity. Urine KIM-1 increased during vancomycin treatment, but its mean values did not differ significantly within ($P = 0.070$) or between ($P = 0.179$) patients with and without nephrotoxicity. Urine KIM-1 accuracy in detecting vancomycin nephrotoxicity was significantly lower than that of serum creatinine at days 5, 7, and 10 of treatment.

Conclusions: Vancomycin nephrotoxicity is common but usually reversible and has readily manageable adverse effect. Urine KIM-1 was not more accurate than serum or urine creatinine in detecting vancomycin nephrotoxicity in our study population.

Keywords: Urine, Kidney Injury Molecule 1, Vancomycin, Nephrotoxicity

1. Background

Vancomycin is a glycopeptide antibiotic that has been used in clinical practice for more than 50 years for the treatment of resistant gram positive infections, especially methicillin-resistant *Staphylococcus aureus* (1). However, vancomycin is associated with a number of adverse effects, including nephrotoxicity. Major features of vancomycin nephrotoxicity are increased serum creatinine level and decreased glomerular filtration rate (GFR) (2). Certain aspects of vancomycin nephrotoxicity, particularly its asso-

ciated factors, have not been studied well in relevant investigations from the Iranian population.

Optimal management and prevention of clinical and economic complications of acute kidney injury (AKI) due to different medications including vancomycin requires early detection of kidney injury (3). Serum creatinine as a classic marker of kidney function suffers from several drawbacks in clinical practice. These include the potential effects of non-renal factors, the non-linear relationship between serum creatinine and GFR, and potential overestimation of renal function in the early phases of AKI (4, 5).

Numerous novel biomarkers of renal function have been investigated in the recent two decades, such as kidney injury molecule-1 (KIM-1) (4).

KIM-1 is a type-1 transmembrane protein that is not detectable in healthy kidney tissue (6). However, its transcription is strongly up-regulated in proximal tubule epithelial kidney cells after ischemic or toxic injury. KIM-1 has been suggested to play a role in the regeneration processes after epithelial injury and removal of dead cells from tubular lumen (4, 7). The utility of KIM-1 has been investigated in several experimental models of kidney injury caused by agents such as cisplatin, gentamicin, vancomycin, furosemide, doxorubicin, tacrolimus, and heavy metals. However, the role of urine KIM-1 in detecting nephrotoxicity caused by medications in clinical settings thus far has only been studied for cisplatin, gentamicin, and amphotericin b (8). In addition to the limited studies in humans, the results are controversial and inconclusive.

2. Objectives

The aims of the present study were to 1) determine the incidence, time onset, and possible associated factors of vancomycin nephrotoxicity and 2) compare the changing patterns and the accuracy of urine KIM-1 and that of serum and urine creatinine in hospitalized patients with hematological and oncological diseases in Shiraz, southwest of Iran.

3. Methods

3.1. Study Setting and Sample Size

During 9 months from August, 2015 to April, 2016, a longitudinal study (ID: 94-01-05-9624) was performed at two hematology-oncology wards (22 beds) and one hematopoietic stem cell transplantation ward (11 beds) of the Namazi hospital, which is a governmental, tertiary, referral, general, 50-ward, 1,000-bed health-care setting affiliated with the Shiraz University of Medical Sciences in Shiraz, Iran. The medical ethics committee of the hospital approved the study, and written informed consent was obtained from all patients. By considering $\alpha = 0.05$, 80% power ($1 - \beta = 0.8$), and the average frequency of vancomycin nephrotoxicity of 20%, a necessary sample size of at least 50 patients was calculated.

3.2. Study Population and Patient Selection

Patients with the following characteristics were recruited: > 18 years, no documented history of AKI (defined an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours, an increase in serum creatinine by ≥ 1.5 times the

baseline within the prior 7 days, or urine volume < 0.5 mL/kg/h for 6 hours) (9) or chronic kidney disease (defined as clearance creatinine below 60 mL/min/1.73 m² or documented history of regular peritoneal or hemodialysis for more than 3 months) (10), no documented history of receiving vancomycin within the past 14 days, and scheduled to receive vancomycin for at least 1 week.

3.3. Data Collection

Required demographics (age, sex, weight) and clinical data (vancomycin dose, duration of treatment, duration of infusion, indication, type of co-administered medications that may exacerbate nephrotoxicity, hospital stay, and mortality) of patients were recorded by an educated pharmacist.

3.4. Biochemical and Serological Measurements

During the course of vancomycin treatment, serum creatinine, sodium, and urea were monitored daily in accordance with the routine practices of the wards. Urine samples for determination of sodium, urea, creatinine, and KIM-1 were collected at days 0, 3, 5, 7, 10, and 14 of vancomycin treatment. Urine samples were stored in a freezer at -80°C (New Brunswick Scientific, Switzerland) until completion of the sampling procedure. Measurement of serum, urine creatinine, sodium, and urea was performed by an auto-analyzer (Shanghai Xunda Medical Instrument, China). Urine levels of KIM-1 were determined by the double sandwich ELISA technique (Bioassay Technology Laboratory, Shanghai, China) using an ELISA-Reader (Denley-WeScan, United States), as previously described (11). All of the above equipments were calibrated.

3.5. Study Endpoints

Vancomycin nephrotoxicity was defined as either a 0.5 mg/dL or > 1 mg/dL elevation in serum creatinine if the initial serum creatinine was ≤ 3 mg/dL or > 3 mg/dL, respectively (2). Either fractional excretion of sodium > 2% or fractional excretion of urea > 50% (in cases of loop diuretic co-administration) was considered as acute tubular necrosis (ATN) (12). Any measure for the management of vancomycin nephrotoxicity including daily dose reduction, alternate day dosing, discontinuing the agent, performing dialysis, or switching to another medication was recorded.

3.6. Statistical Analyses

Continuous data were expressed as mean \pm standard deviation (SD). Categorical variables were reported as percentages. Chi-square or Fisher's exact test (if > 25% of the categories has expected frequencies < 5) were exploited

to evaluate possible associations among categorical variables. Continuous variables were analyzed by independent t-test. Logistic regression analysis with odds ratio (OR) and a 95% confidence interval (CI) using the "stepwise" method were used to determine associated factors of vancomycin nephrotoxicity. In the first step, the possible association of each independent variable including age, gender, cumulative dose of vancomycin, vancomycin indication, baseline GFR value, co-administration of aminoglycosides, calcineurin inhibitors, amphotericin b, acyclovir, and loop diuretics with vancomycin nephrotoxicity (as dependent variable) was assessed separately by an univariate analysis. Variables with P values less than 0.3 were then considered together for multivariate logistic regression analysis. One-way analysis of variance (ANOVA) with repeated measures was exploited for comparison of the mean values of studied biomarkers at days 0, 3, 5, 7, 10, and 14 of treatment within and between patients with and without vancomycin nephrotoxicity. The accuracy of serum creatinine, urine creatinine, and urine KIM-1 at days 0, 3, 5, 7, and 10 of treatment in detecting vancomycin nephrotoxicity was evaluated by the receiver operating characteristic (ROC) curves of sensitivity and specificity, and relevant data were expressed in terms of area under the curve (AUC) and 95% confidence intervals (CI). Statistical significance in all analyses was defined by P values < 0.05, except for the first step of logistic regression analysis (P values < 0.3). All of the above statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) version 20 software (IBM company, New York, NY, United States).

4. Results

During the study period, 71 patients were scheduled to receive vancomycin. Among these, 52 individuals were recruited. In contrast, 19 patients did not meet the inclusion criteria due to one or more of the following reasons: discharged from the hospital or transferred to another ward (n = 10), receiving vancomycin for less than one week due to change in diagnosis (n = 1) or adverse effects (n = 4), and died before one week of vancomycin treatment (n = 4). There was no missing data for the included 52 patients.

The mean \pm SD age of the study population was 43.38 ± 16.46 years. There were 35 male patients and 18 female patients. The 3 most common admission diagnoses of patients were acute myeloid leukemia (48.08%), acute lymphoid leukemia (15.38%), and non-Hodgkin's lymphoma (7.69%). Vancomycin indications were febrile neutropenia (86.54%), sepsis (7.69%), hospital acquired pneumonia (3.85%), and cellulitis (1.92%). The mean \pm SD daily and cumulative doses of vancomycin were 1.75 ± 0.65

g and 26.57 ± 16.41 g, respectively. All courses of vancomycin administration were infused within 1 hour. Duration of vancomycin treatment ranged between 7 and 36 days. Potential nephrotoxic medications including acyclovir, amphotericin B, loop diuretics (furosemide), calcineurin inhibitors (cyclosporine), and chemotherapeutic agents (high dose methotrexate) were administered to 43 (82.69%), 22 (42.31%), 8 (15.38%), 5 (9.62%), and 4 (7.69%) patients, respectively. No patient received cisplatin, ifosfamide, cyclophosphamide, aminoglycosides, cephalosporins, piperacillin-tazobactam, or tenofovir during the study period.

Among the cohort, 13 (25%) and 33 (63.46%) patients developed vancomycin nephrotoxicity and ATN, respectively. The mean \pm SD onset of vancomycin nephrotoxicity was 11.46 ± 7.56 days. Its minimum and maximum values were 4 and 26 days, respectively. According to univariate analysis, vancomycin cumulative dose (P = 0.087), chemotherapeutic agents co-administration (P = 0.251), cyclosporine co-administration (P = 0.08), and furosemide-co-administration (P = 0.015) were selected. After adjusting for selected variables in the multivariate logistic regression model, only furosemide-co-administration (OR = 0.126 [95%CI = 0.023 - 0.694], P = 0.017) was significantly associated with vancomycin nephrotoxicity (Table 1).

Among the 13 patients who developed vancomycin nephrotoxicity, 5 experienced spontaneous resolution without any intervention. In contrast, vancomycin nephrotoxicity continued until death in 1 subject. In the remaining 7 individuals, time intervals of vancomycin administration were increased from every 12 hours to every 72 hours or once weekly (n = 5), or vancomycin was switched to teicoplanin (n = 2). No patient underwent emergent hemodialysis due to vancomycin nephrotoxicity. There was no statistically significant difference in the duration of hospitalization between patients with and without vancomycin nephrotoxicity (34.92 ± 14.07 days and 30.02 ± 9.99 days, respectively; P = 0.175). Similarly, the mortality rate was comparable between patients with (30.77%) and without (28.21%) vancomycin nephrotoxicity (P = 1).

The changing pattern of serum creatinine, urine creatinine, and urine KIM-1 values at the studied time points during vancomycin treatment is depicted in Figure 1. The overall change in the mean (95% CI) values of serum creatinine, urine creatinine, and urine KIM-1 were not statistically significant within patients with and without AmB nephrotoxicity (P = 0.058, P = 0.116, and P = 0.070, respectively). In addition, neither the overall changes in the mean (95% CI) values of urine creatinine (P = 0.068) or urine KIM-1 (P = 0.179) between the two groups were statistically significant. In contrast, the mean (95% CI) difference of serum

Table 1. Comparison of Different Demographic and Clinical Features of the Study Population (n = 52) within Patients With and Without Vancomycin Nephrotoxicity

Variable	With Nephrotoxicity (n = 13)	Without Nephrotoxicity (n = 39)	Univariate Model	Multivariate Model		
			P Value	OR (95% CI)	P Value	OR (95% CI)
Age, y			0.628	0.990 (0.952 - 1.030)	-	-
Mean ± SD	41.46 ± 14.32	44.0 ± 17.24				
Range	23 - 66	20 - 81				
Gender, %			0.316	1.929 (0.533 - 6.972)	-	-
Male	7 (53.85)	27 (69.23)				
Female	6 (46.15)	12 (30.77)				
Baseline glomerular filtration rate, ml/min/1.73m²			0.716	1.002 (0.989 - 1.016)	-	-
Mean ± SD	118.07 ± 44.79	112.81 ± 46.14				
Range	54.05 - 223.97	51.44 - 301.39				
Vancomycin indication, %			0.815	1.236 (0.210 - 7.296)	-	-
Treatment of febrile neutropenia	11 (84.62)	34 (87.18)				
Others	2 (15.38)	5 (12.82)				
Vancomycin treatment duration, d			0.306	1.048 (0.958 - 1.147)	-	-
Mean ± SD	16.85 ± 6.57	14.61 ± 6.82				
Range	8 - 27	7 - 36				
Vancomycin cumulative dose, g			0.087	0.961 (0.918 - 1.006)	0.503	0.985 (0.941-1.030)
Mean ± SD	19.69 ± 21.63	28.87 ± 13.85				
Range	16 - 54	14 - 72				
Co-administration of acyclovir, %			0.528	1.650 (0.348 - 7.821)	-	-
Yes	10 (76.92)	33 (84.62)				
No	3 (23.08)	6 (15.38)				
Co-administration of amphotericin b, %			0.334	0.536 (0.151 - 1.902)	-	-
Yes	7 (53.85)	15 (38.46)				
No	6 (46.15)	24 (61.54)				
Co-administration of furosemide, %			0.015	0.133 (0.026 - 0.676)	0.017	0.126 (0.023 - 0.694)
Yes	5 (38.46)	3 (7.69)				
No	8 (61.54)	36 (92.31)				
Co-administration of cyclosporine, %			0.080	0.180 (0.026 - 1.230)	1.0	3.93 (0.485 - 11.723)
Yes	3 (23.08)	2 (5.13)				
No	10 (76.92)	37 (94.87)				
Co-administration of chemotherapeutic agents, %			0.251	0.297 (0.037 - 2.361)	1.0	4.28 (0.989 - 16.537)
Yes	2 (15.38)	2 (5.13)				
No	11 (84.62)	37 (94.87)				

creatinine between patients with and without vancomycin nephrotoxicity reached the level of statistical significance (0.472 [0.159 to 0.784], P = 0.005). According to Tables 2 - 4, the mean (95% CI) changes in serum creatinine, urine creatinine, and urine KIM-1 values at each two studied time points were comparable between patients with and without vancomycin nephrotoxicity.

Analysis of ROC curves of sensitivity and specificity demonstrated that AUC (95% CI) of serum creatinine at days 5 [0.721 (0.551 to 0.891), P = 0.018], 7 [0.764 (0.599 to 0.929), P = 0.006], and 10 [0.885 (0.735 to 1.0), P = 0.001] of vancomycin treatment was significantly higher than that of urine creatinine and urine KIM-1. In contrast, these values were comparable at days 0 and 3 (Table 5, Figure 2). Cal-

culating AUC values of studied renal biomarkers was not statistically feasible at day 14 of vancomycin treatment due to the fact that urine samples of only 19 patients were available at this time point.

5. Discussion

The rate of vancomycin nephrotoxicity in our cohort (25%) was within the range reported in the literature. The incidence of vancomycin-induced nephrotoxicity ranged between 5% and 35% in mono- and combination therapy, respectively (2). At the same hematology-oncology ward of the Namazi Hospital between 2008 and 2009, Vazin et al. demonstrated that 35% of vancomycin recipients experienced a rise in serum creatinine of greater than 0.5

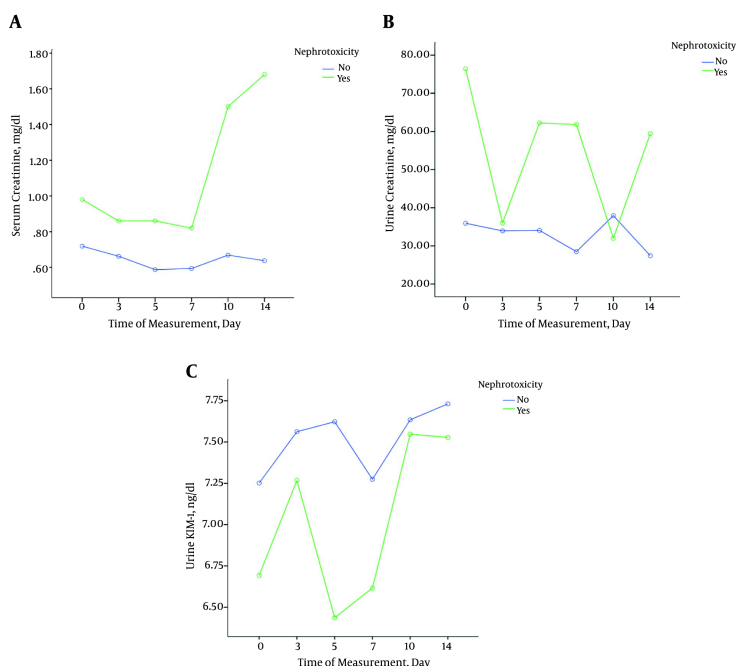


Figure 1. The Changing Pattern of A, Serum Creatinine; B, Urine Creatinine; C, Urine KIM-1 at Days 0, 3, 5, 7, 10, and 14 of Vancomycin Treatment in Patients With and Without Nephrotoxicity

Table 2. Mean (95% Confidence Interval) Difference in Serum Creatinine Values at Studied Time Points During Vancomycin Treatment Between Patients With and Without Nephrotoxicity

Time Point	Day 0	Day 3	Day 5	Day 7	Day 10	Day 14
Day 0	*	0.088 (-0.087 to 0.263) [1]	0.126 (-0.011 to 0.263) [0.093]	0.142 (-0.047 to 0.332) [0.309]	-0.235 (-0.831 to 0.361) [1]	-0.309 (-1.037 to 0.418) [1]
Day 3	-	*	0.037 (-0.119 to 0.194) [1]	0.054 (-0.141 to 0.250) [1]	-0.323 (-0.867 to 0.221) [0.915]	-0.398 (-1.071 to 0.276) [0.934]
Day 5	-	-	*	0.017 (-0.084 to 0.118) [1]	-0.361 (-0.917 to 0.195) [0.636]	-0.435 (-1.121 to 0.251) [0.703]
Day 7	-	-	-	*	-0.378 (-0.923 to 0.168) [0.473]	-0.452 (-1.134 to 0.231) [0.581]
Day 10	-	-	-	-	*	-0.074 (-0.260 to 0.111) [1]
Day 14	-	-	-	-	-	*

mg/dL (13). The rate of vancomycin-induced nephrotoxicity (no definition was provided by the authors) in a referral infectious diseases ward of Imam Khomeini hospital in Tehran in 2004 was 17.5% (14). In the same ward in 2013, Khalili et al. reported that 7.4% of patients who received vancomycin alone developed AKI based on the Acute Kidney Injury Network (AKIN) criteria. However, the rates of AKI in patients given the combination of vancomycin plus amikacin, vancomycin plus amphotericin, and vancomycin plus amphotericin plus ceftriaxone were 40%, 100%, and 100%, respectively (15). Finally, in a random-

ized clinical trial on conventional- (15 mg/kg twice a day) versus high-dose (15 mg/kg three times a day) vancomycin regimens in patients with acute bacterial meningitis, no patients developed nephrotoxicity (defined as a 50% decrease in creatinine clearance or an increase in serum creatinine of 0.5 mg/dL or more) (16). Apart from the presence of risk factors (especially concomitant medications), different study methodologies, clinical settings, and AKI definitions can account for the variation in the incidence of vancomycin nephrotoxicity in the above studies. Regarding the last issue, it is noteworthy that the definition of van-

Table 3. Mean (95% Confidence Interval) Difference in Urine Creatinine Values at studied Time Points During Vancomycin Treatment Between Patients With and Without Nephrotoxicity

Time Point	Day 0	Day 3	Day 5	Day 7	Day 10	Day 14
Day 0	*	21.2 (0.958 to 41.442) [0.35]	8.038 (-19.035 to 35.110) [1]	11.019 (-14.11 to 36.147) [1]	21.2 (-19.858 to 62.258) [1]	12.750 (-12.308 to 37.808) [1]
Day 3	-	*	-13.162 (-33.327 to 7.002) [0.619]	-10.181 (-21.062 to 0.699) [0.081]	0.000 (-32.337 to 32.337) [1]	-8.450 (-27.642 to 10.742) [1]
Day 5	-	-	*	2.981 (-14.739 to 20.701) [1]	13.162 (-15.676 to 42.001) [1]	4.712 (-23.645 to 33.07) [1]
Day 7	-	-	-	*	10.181 (-23.148 to 43.510) [1]	1.731 (-22.139 to 25.601) [1]
Day 10	-	-	-	-	*	-8.450 (-40.122 to 23.222) [1]
Day 14	-	-	-	-	-	*

Table 4. Mean (95% Confidence Interval) Difference in Urine Kidney Injury Molecule 1 Values at Studied Time Points During Vancomycin Treatment Between Patients With and Without Nephrotoxicity

Time point	Day 0	Day 3	Day 5	Day 7	Day 10	Day 14
Day 0	*	-0.443 (-1.299 to 0.412) [1]	-0.057 (-1.288 to 1.173) [1]	0.027 (-1.267 to 1.320) [1]	-0.619 (-1.760 to 0.521) [1]	-0.658 (-1.879 to 0.564) [1]
Day 3	-	*	0.386 (-0.405 to 1.177) [1]	0.470 (-0.457 to 1.397) [1]	-0.176 (-1.022 to 0.670) [1]	-0.214 (-1.238 to 0.810) [1]
Day 5	-	-	*	0.084 (-0.355 to 0.523) [1]	-0.562 (-1.404 to 0.280) [0.550]	-0.600 (-1.495 to 0.294) [0.537]
Day 7	-	-	-	*	-0.646 (-1.589 to 0.297) [0.488]	-0.684 (-1.640 to 0.271) [0.395]
Day 10	-	-	-	-	*	-0.038 (-0.623 to 0.547) [1]
Day 14	-	-	-	-	-	*

Table 5. Comparison of Area Under the Curve (95 % Confidence Interval) of Serum Creatinine, Urine Creatinine, and Urine KIM-1 at Days 0, 3, 5, 7, and 10 of Vancomycin Treatment in Detecting Nephrotoxicity

Variable	Day 0		Day 3		Day 5		Day 7		Day 10	
	AUC (95%CI)	P Value	AUC (95%CI)	P Value	AUC (95%CI)	P Value	AUC (95%CI)	P Value	AUC (95%CI)	P Value
Serum creatinine	0.528 (0.346 - 0.709)	0.767	0.667 (0.49 - 0.844)	0.074	0.721 (0.551 - 0.891)	0.018	0.764 (0.599 - 0.929)	0.006	0.885 (0.735 - 1.0)	0.001
Urine creatinine	0.612 (0.443 - 0.781)	0.228	0.549 (0.383 - 0.716)	0.597	0.673 (0.511 - 0.835)	0.064	0.607 (0.426 - 0.787)	0.267	0.517 (0.307 - 0.727)	0.880
Urine KIM-1	0.378 (0.208 - 0.547)	0.190	0.310 (0.143 - 0.477)	0.41	0.269 (0.114 - 0.425)	0.13	0.395 (0.232 - 0.558)	0.277	0.528 (0.307 - 0.749)	0.806

comycin nephrotoxicity exploited in our study is the most commonly used one in the relevant literature (2).

The onset of vancomycin nephrotoxicity in the present study (11.46 ± 7.56 days) was comparable to that reported by other investigations. This value typically ranges from 4 to 8 days after the initiation of vancomycin treatment (17). In a study at Albany medical center hospital in the United States between 2005 and 2006, AKI occurred at least 12 days after vancomycin administration (18). The median time to the development of vancomycin nephrotoxicity was 9 days in another retrospective study from the United States (19). In relevant studies from Iran discussed above, only Khalili et al. noted and reported the on-

set of vancomycin nephrotoxicity. It was 18.6 ± 5.7 days and 4.2 ± 1.3 days in patients who received vancomycin alone and vancomycin plus aminoglycoside combination, respectively. This difference was statistically significant ($P = 0.03$). Therefore, it appears that vancomycin nephrotoxicity developed sooner in combination therapy than in monotherapy (15). Given that none of our patients received aminoglycosides during the study period, evaluating this issue was not feasible.

Among different studied demographic and clinical variables in our population, only furosemide co-administration ($OR = 0.126$ [95% CI = 0.023 - 0.694], $P = 0.017$) was significantly associated with vancomycin

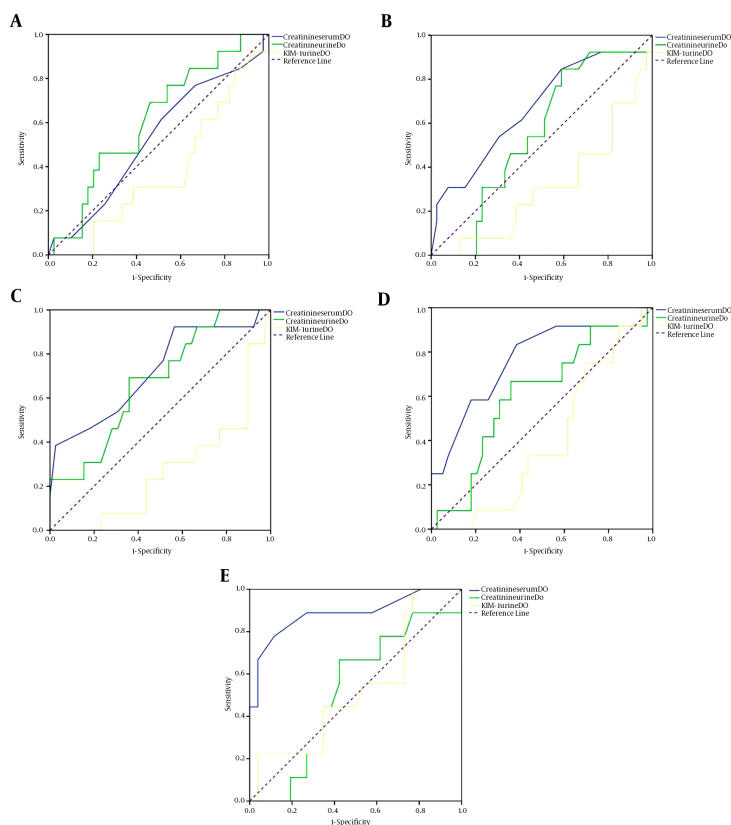


Figure 2. Receiver Operating Characteristic Curves of Sensitivity and Specificity of Serum Creatinine, Urine Creatinine, and Urine KIM-1 at Days A, 0; B, 3; C, 5; D, 7, E, 10 of Vancomycin Treatment for Detection of Nephrotoxicity

nephrotoxicity based on multivariate logistic regression analysis. In line with our results, high troughs (≥ 15 mg/L) and receiving furosemide in the intensive care unit were identified as risk factors of vancomycin nephrotoxicity at a children’s hospital in the United States (20). Similarly, Moh’d et al. reported that concurrent use of loop diuretics, along with admission to the intensive care unit and cirrhosis co-morbidity, were significantly associated with vancomycin nephrotoxicity (19). Another retrospective, single-center, observational cohort study demonstrated that the rate of loop diuretic administration was higher in patients with (62.5%) than those without (44.4%) vancomycin nephrotoxicity ($P = 0.083$) (21). Other suggested risk factors of vancomycin nephrotoxicity are old age, impaired baseline renal function, longer duration of therapy, intermittent infusion (versus continuous infusion), high trough level, and co-administration of piperacillin-tazobactam, aminoglycosides, and vasoactive drugs (2, 17, 22). However, the association of these variables with the development of vancomycin nephrotoxicity has not been demonstrated consistently in relevant studies. As noted by

Costa e Silva et al., risk factors for vancomycin nephrotoxicity remain a matter of debate despite the performance of several investigations in this regard. This may be partially due to fact that most of the evidence related to risk factors for vancomycin is derived from observational studies, and only a few randomized clinical trials with small numbers of patients have been conducted so far (23).

Regarding clinical outcome, vancomycin nephrotoxicity resolved spontaneously in nearly two-fifths (38.46%) of our population. Furthermore, length of hospital stay and mortality rates were comparable between patients with and without nephrotoxicity. Vancomycin nephrotoxicity is usually considered to be reversible. If the medication is discontinued or doses are adjusted immediately, persistent kidney damage is uncommon (2). The clinical outcome of vancomycin nephrotoxicity has not been taken into account in relevant studies from Iran. McKamy et al. reported that serum creatinine returned into baseline values in 46% and 75% of pediatric patients by the end of vancomycin therapy and hospital discharge, respectively (20). In contrast to our findings, at least one retrospective study

in adults demonstrated that in-hospital mortality rate ($P = 0.001$) and hospital length of stay ($P = 0.006$) were significantly higher in patients with vancomycin nephrotoxicity compared to those without this adverse effect (21). The presence of confounding factors (e.g., severity of underlying disease) and sample size difference may partially account for these disparities. Although teicoplanin, which is not currently approved for use or available in the United States, has been found to be as effective and less nephrotoxic than vancomycin in a number of clinical studies, systematic reviews, and meta-analyses (24-26), according to at least one more recent meta-analysis of randomized controlled trials in the Chinese population, teicoplanin safety, including nephrotoxicity, was similar to that of vancomycin (27). However, it may be reasonable to consider teicoplanin instead of vancomycin for patients at higher risk of AKI or for those who develop nephrotoxicity during vancomycin treatment.

Although it has an incremental trend, the overall mean difference of urine KIM-1 values during the course of vancomycin treatment was comparable within and between patients with and without nephrotoxicity. This was also true for six studied time points between two groups during vancomycin treatment. In addition, the accuracy of urine KIM-1 in detecting nephrotoxicity was significantly lower than that of serum creatinine at days 5, 7, and 10 of vancomycin treatment. To our knowledge, so far only 5 clinical studies have assessed the role of urine KIM-1 in detecting the nephrotoxicity of medications including cisplatin, gentamicin, and amphotericin b (11, 28-31). In this regard, urine KIM-1 was superior to urine N-acetyl- β -D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), and IL-18 in detecting cisplatin and gentamicin nephrotoxicity in two pediatric studies (28, 29). Shinke et al. determined that among the studied renal biomarkers including urine KIM-1, monocyte chemoattractant protein-1 (MCP-1), NAG, NGAL, and β 2-microglobulin in lung cancer patients receiving cisplatin, KIM-1 and MCP-1, but not NGAL, NAG, or β 2-microglobulin values, were significantly higher in patients with AKI than those without AKI. They also reported that urinary KIM-1 and MCP-1 had significantly higher accuracy than urinary NGAL in detecting AKI in patients receiving cisplatin (31). In contrast to these data, at least one clinical trial on N-acetylcysteine's ability to prevent amphotericin B-induced nephrotoxicity demonstrated that the changes in mean urine KIM level during amphotericin B treatment within and between treatment groups were not statistically significant. The accuracy of urine KIM-1 at days 0 and 7 of amphotericin B treatment in detecting nephrotoxicity was comparable with that of serum and urine creatinine (11). Our negative findings can be justified by our relatively small sample

size (lack of statistical power for identifying the true difference), limited measurements of urine KIM-1 (only six time points), and using certain serum creatinine cut points rather than GFR calculated by a gold standard method, such as an exogenous agent for determining nephrotoxicity. The considerable rate of ATN (63.46%) in our study population precludes this idea that urine KIM-1 (as a marker of proximal tubule ischemia) did not increase significantly during vancomycin treatment because ATN may not occur within the follow-up period.

The major novelty and strength of the current investigation is determining different aspects (including clinical outcomes) and associated factors of vancomycin nephrotoxicity not previously studied in Iran. Furthermore, to the best of our knowledge, we studied the changing pattern and accuracy of KIM-1 in urine in vancomycin recipients for the first time. Aside from the relatively small sample size (due to considering several exclusion criteria and the preference of teicoplanin over vancomycin by some hematologist-oncologists) and the limited number of urine KIM-1 measurements for each patient (due to financial problems), lack of data about the trough level of vancomycin (as one of the most notable potential risk factors of vancomycin nephrotoxicity) due to practical and financial problems can be considered a main drawback of our study. The other concerning issue is the degradation plausibility of studied renal biomarkers, especially KIM-1, during the storage period at -80°C since the measurement of urinary renal biomarkers was postponed until completing the sampling process of all patients. The package insert of the KIM-1 kit provided by the manufacturer does not consider this matter. However, Pennemans et al. demonstrated that if urine samples collected for KIM-1 measurements are frozen within 3 hours after voiding, they remain stable for up to 1.5 years at -80°C (32). Similarly, another study reported that if urine samples are immediately cooled to 4°C and subsequently frozen at -80°C within 2 days, urine KIM-1 levels are stable for at least 6 months (33). Therefore, adverse effects of storage conditions (up to 9 months at -80°C) on the value of urine KIM-1 seem unlikely.

In conclusion, one-fourth (25%) of our cohort developed nephrotoxicity, usually within the first 2 weeks of vancomycin treatment. Among the studied demographic and clinical variables, only furosemide co-administration was significantly associated with vancomycin nephrotoxicity, which resolved spontaneously in nearly two-fifths (38.46%) of involved individuals. Mortality and duration of hospitalization were comparable between patients with and without vancomycin nephrotoxicity. Urine KIM-1 tended to increase during vancomycin treatment, but its mean values did not differ significantly within and between patients with and without nephrotoxicity. The accuracy of

urine KIM-1 levels in detecting vancomycin nephrotoxicity was significantly lower than that of serum creatinine at days 5, 7, and 10 of treatment. Although vancomycin nephrotoxicity is a common adverse effect, it appeared to be mostly reversible and readily manageable by adjusting the dose or switching to less nephrotoxic agents in our study population. More studies with adequate sample size and more frequent sampling times are warranted to elucidate the role of new biomarkers of renal function, such as urine KIM-1, in the early detection of vancomycin nephrotoxicity and assessing renal function in vancomycin recipients.

Footnote

Authors' Contribution: Iman Karimzadeh contributed to the study design, data analysis, and manuscript review. Ghazaleh Haghighati contributed to patient selection, data gathering, and manuscript drafting. Mani Ramzi contributed to study design and manuscript review. Mohammad Mahdi Sagheb contributed to clinical interpretation of data and manuscript review. Kamiar Zomorodian contributed to biochemical and serological measurements and manuscript review.

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