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Comparing Effects of Different Doses of Vancomycin on the Biomarkers of Acute Kidney Injury

Sepideh Elyasi[1*], Hossein Khalili[2], Alireza Abdollahi[3]

[1]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Pathology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background: Various urinary and serum proteins are being studied for detection of early stages of drug-induced nephrotoxicity like Gamma-glutamyltransferase (GGT), glutathione-S-transferase (GST), N-acetyl-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (Cys-C), and kidney injury molecule 1 (KIM-1). As vancomycin nephrotoxicity is an important adverse reaction related to its high dose, its early diagnosis is vital. So in this study, effects of different vancomycin dosing on two renal biomarkers (Cys-C and KIM-1) of acute kidney injury and also serum creatinine were compared in patients with severe bacterial infections.

Methods: Fifty-eight patients with severe infections requiring vancomycin therapy, randomly received vancomycin 1g/ twice daily (N=29) or 1g/ three times daily (N=29). Serum levels of Cys-C and KIM-1 and urine level of Cys-C were measured at baseline and every other and compared between two groups.

Results: Serum level of Cys-C demonstrated significant rise during vancomycin treatment in both groups. However, there was no significant difference between them. Urine Cys-C level neither changed significantly within nor between groups during vancomycin treatment. The same results were detected for serum KIM-concentrations.

Conclusion: Different doses of vancomycin showed comparable effects on the serum and urine biomarkers of acute kidney injury. So, it seems that increasing vancomycin dose to 15mg/kg three times a day may not significantly increase risk of nephrotoxicity.

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Introduction

A daily vancomycin dose of 15 to 20 mg/kg every 8 or 12 hours to maintain its trough serum concentration between 15 and 20 mg/L is recommended for the treatment of methicillin resistance staphylococcus aureus (MRSA) infections (1-2). Despite its effectiveness against gram-positive infections, vancomycin can potentially cause adverse reactions such as nephrotoxicity and ototoxicity (3-4). Nephrotoxicity is an old but concerning adverse reaction of vancomycin, which was reported in 5% to 35% of patients (4-6). Achieving vancomycin trough levels higher than 15-20 mg/L or administration of doses above 4 g/day increased the risk of vancomycin-induced nephrotoxicity, especially in presence of other predisposing factors (7-9). Therapeutic drug monitoring (TDM) is recommended as a valuable approach for preventing vancomycin-induced nephrotoxicity and reaching favorable clinical outcome. Nevertheless, there is lack of conclusive correlation between vancomycin serum concentration and vancomycin-induced nephrotoxicity (10-11). In most previous studies, acute kidney injury (AKI)

*Corresponding Author: Dr Sepideh Elyasi
Address: Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, 91775-1365, Iran. Tel:+985131801588, Fax: +985131801592.
E-mail: Elyasis@mums.ac.ir

has been defined as a 0.5 mg/dL elevation in serum creatinine (Scr) if the initial Scr was ≤3 mg/dL, or a rise of >1 mg/dL if the initial Scr was >3 mg/dl (6, 12). However, Serum creatinine (Scr), as well as other traditionally used markers of renal injury, including blood urea nitrogen, urine sediment, and urinary indices is not a sensitive, reliable and accurate marker of renal function, since it is easily affected by a number of non-renal factors such as the amount of muscle, gender, age, race, physical activity and nutritional status. Numerous urinary and serum proteins are being studied for detection of early stages of drug-induced nephrotoxicity. Gamma-glutamyltransferase (GGT), glutathione-S-transferase (GST), N-acetyl-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (Cys-C), kidney injury molecule 1 (KIM-1), and L-type fatty acid-binding protein are some of these biomarkers (13-21).

Considering the controversies regarding safety of higher doses of vancomycin, nephrotoxicity of 15-20mg/kg BD & TDS dosing of vancomycin was compared based on the novel biomarkers of renal function (Cys-C and KIM-1) in patients with severe MRSA infections.

Methods

This is an open-label randomized parallel clinical trial which performed from September 2012 until September 2013. During 12 months period, 70 patients with the diagnosis of severe bacterial infections including blood stream infection, acute bacterial endocarditis, acute bacterial meningitis and pneumonia based on the clinical, microbiological and laboratory data, admitted to infectious diseases ward of Imam Khomeini hospital in Tehran, Iran, planned to receive antibacterial regimen consist of vancomycin, were screened. The antibiotic regimens were started within 4-hours of suspected severe infections. Patients with age less than 18 years, renal failure (defined as clearance creatinine below 60 ml/min/1.73m2, history of peritoneal or hemodialysis for more than 3 months), proteinuria (albumin excretion rate ≥30mg/24 hours in diabetic and non-diabetic individuals), positive sample cultures other than MRSA infection and with alternative diagnosis were excluded. Fifty eight patients with positive culture for MRSA or negative culture who meet the inclusion criteria of the study were included into this randomized, open-label, prospective clinical study. The study was registered in Tehran University of Medical Sciences (9-Sep-2013-T-66).

Recruited patients were randomly assigned to receive vancomycin either 15 mg/kg every 12 hours (low dose group) or 15 mg/kg every 8 hours (high dose group). Computer generated list of sequential random allocation was produced. Then, block randomization of four patients was used to ensure balanced allocation of eligible patients in two arms. In both groups, patients received each dose of vancomycin as slow intravenous infusion (15mg/min). None of the patients received vancomycin loading dose.

Required the patients' demographic and clinical data including sex, age, weight, height, underlying diseases, drug history and concomitant diseases and treatments were collected from the patients' medical records. Laboratory parameters including Scr, BUN, cell blood count (CBC), CRP, and ESR were monitored periodically and vital signs were evaluated daily.

At baseline and then every other day, during the first 8 days of vancomycin treatment, 10 ml venous blood sample was collected from each recruited patient to measure serum Cys-C, and KIM-1. Simultaneously, 10 ml urine (from each patient's 8-hour urine collection at night) was also isolated for determining urine Cys-C level. A 5 ml venous blood sample was collected from each individual exactly before starting infusion of 4th dose of vancomycin and morning dose of vancomycin in 10th day of treatment for measurement of vancomycin serum trough level. Serum trough level of vancomycin was measured by the fluorescence polarization method. Vancomycin serum trough levels between15 to 20 mg/L were considered as therapeutic.

Serum and urine levels of Cys-C were measured by the Cys-C kit (Gentian, Moss, Norway) using the turbidimetric method. In this type of assay, 3 µL of diluted samples (urine or serum) was mixed with 220 µL reaction buffer [3-(N-Morpholino)-propane sulfonic acid buffered saline]. The samples then incubated for 120 seconds. In next step, 45 µL immunoparticle aggregate containing avian anti-human Cys-C antibodies were added to the admixture. Light absorption of the admixture was determined at 550 nm wavelength 300 seconds after the reaction.

Serum level of KIM-1 was determined by the double sandwich ELISA technique (Bioassay Technology Laboratory, Shanghai, China). Urine samples were centrifuged for 20 minutes and then 40 µL of the supernatant along with 10 µL anti-KIM-1 antibodies and 50 µL Streptavidin-Horseradish Peroxidase conjugate were transferred to the well. In next step, at least 0.35 mL diluted washing solution with distilled water was added to each well. After 1-2 minutes, 50 µL chromogen solution A and 50 µL chromogen solution B were added. Following incubating for 10 minutes at 37°c, 50 µL stop solution was added to each well and light absorption of the admixture in each well was determined at 450 nm wavelength.

Statistical Package for the Social Sciences (SPSS) version 11.5 (SPSS Inc., USA) was used for all descriptive-analytical analyses. Continuous data were expressed as mean ± standard deviation (SD) and categorical data were shown as percentage. Independent t-test and chi-square test (or Fisher's exact test in cases which more than 25% of categories had expected

frequencies under 5) were used for the comparison of patients' continuous and categorical data, respectively. Trend of serum levels of Cys-C, and KIM-1 and also urine levels of Cys-C changes during the treatment course were assessed by the repeated-measures analysis of variance. P-values less than 0.05 were considered statistically significant.

Results

Seventy patients were evaluated for inclusion in this study. Excluding 8 patients for underlying renal disease, two patients for receiving concomitant nephrotoxic drugs and two patients for not signing the written consent form, finally fifty-eight patients completed the study (29 patients in each group) (Figure 1). Demographic and baseline clinical characteristics of patients in the low and high dose groups have been summarized in Table 1. Cardiovascular diseases (36%) were the most common type of concomitant diseases. Among co-administered medications, cardiovascular agents (30%) were the most frequent class in this cohort.

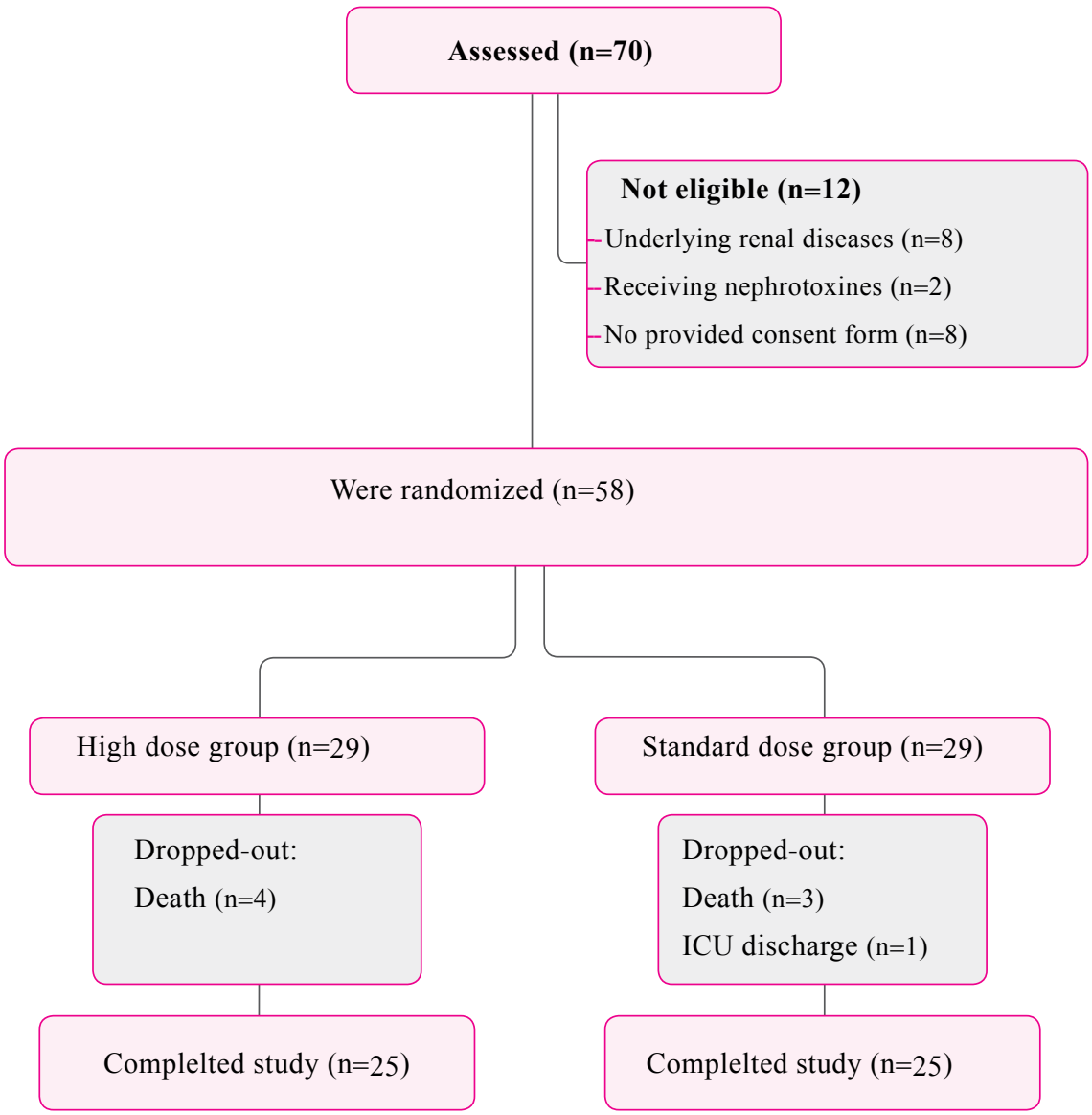

Figure 1. Consort flow-chart of the study.

Table 1. Baseline data of patients in conventional and high dose groups.

Variable	Conventional dose	High dose	P value
Age, year (mean ± SD)	56±24.34	53.05±20.74	0.80
Male (%)	65	75	0.22
Weight, kg (mean ± SD)	68.5±11.48	72.75±8.98	0.21
BMI, kg/m2 (mean ± SD)	24.03±2.25	24.02±2.06	0.99
Mean arterial pressure (mmHg)	75.03±1.22	77.19±2.11	0.23
Heart rate (beats/min)	115.66±24.15	120.33±30.95	0.11
Respiratory rate (breaths/min)	28.04±8.55	27.78±9.44	
Oxygen saturation (%),without oxygen support	89.35±20.34	85.67±19.59	0.20
Scr, mg/dl (mean ± SD)	0.99±0.4	1.02±0.19	0.76
Temperature, °C (mean ± SD)	37.46±0.88	37.19±0.63	0.27
CRP, mg/L (mean ± SD)	55.87±54.11	29.79±19.00	0.16
ESR, mm/h (mean ± SD)	38.8±25.75	51.91±39.82	0.39
Type of infection, n (%) Blood stream infection Acute bacterial endocarditis Acute bacterial meningitis Pneumonia	 10(40) 8(32) 5(20) 2(8)	 11(44) 9(36) 4(16) 1(4)	0.65
Positive culture for MRSA, n (%) Blood CSF Endotracheal suction	 12(48) 2(8) 1 (4)	 13(52) 1(4) 1(4)	0.74
Concomitant drugs, n (%) Meropenem or imipenem Pipracillin-tazobactam Ceftriaxone Cirprofloxacin Cardiovascular drugs Neuropsychiatric drugs* Antidiabetic medications	 3(12) 1(4) 1(4) 2(8) 8(32) 5(20) 4(16)	 2(8) 1(4) 2(8) 3(12) 7(28) 6(24) 4(16)	0.72
Chronic concomitant diseases, n (%) Cardiovascular diseases Diabetes mellitus Neuropsychiatric problems	 10 (40) 6(24) 5(20)	 8(32) 5 (20) 7(28)	0.1

BMI: Body mass index, Scr: Serum creatinine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MRSA: Methicillin-resistant Staphylococcus aureus

*including benzodiazepines and antidepressants

Blood stream infection (42%) followed by acute bacterial endocarditis (34%), acute bacterial meningitis (18%) and pneumonia (6%) were common type of infections in the patients. Cultures were positive for MRSA in 60% of the patients. Carbapenems (20%) followed by ciprofloxacin (10%) were common concomitant administered antibiotics in this cohort. No statistically significant difference regarding the patients' demographic, clinical, and paraclinical characteristics were detected between the groups (conventional versus high dose vancomycin).

Level of serum Cys-C demonstrated significant increased during vancomycin treatment in both groups ($p<0.001$). However, there was no significant difference between two groups regarding serum Cys-C level ($p=0.69$) (Table 2).

Table2. Comparing changes in serum Cystatin-C and KIM-1 and urine Cystatin-C during the study period in the low and high dose vancomycin groups

Parameter	Baseline	Day 2	Day 4	Day6	Day 8	Between group P value	Within group P value
Clcr: CG ((ml/min,), low dose	82.43±27.84 (79.11±20.13)	87.45±27.73 (82.98±23.77)	85.80±34.89 (87.23±40.19)	84.22±11.97 (85.34±18.23)	83.39±13.87 (88.19±22.66)	0.41(0.87)	0.34 (0.10)
Clcr: : CG (ml/min), High dose	89.92±21.69 (93.34±29.45)	85.81±25.07 (87.23±22.09)	86.68±26.18 (85.46±24.57)	86.01±22.12 (89.50±29.33)	85.29±23.62 (87.67±28.90)		
Serum Cystatin-C (mg/L), low dose	0.88±0.23	0.85±0.11	0.92±0.13	1.00±0.23	1.09±0.26	0.69	<0.001
Serum Cystatin-C (mg/L), high dose	1.01±0.25	0.98±0.28	1±0.29	1.07±0.26	1.10±0.11		
Urine Cystatin-C (mg/L), low dose	0.042±0.03	0.043±0.34	0.047±0.03	0.048±0.04	0.050±0.0	0.18	0.08
Urine Cystatin-C (mg/L), high dose	0.035±0.04	0.042±0.03	0.044±0.04	0.048±0.05	0.052±0.02		
Serum KIM-1 level (ng/dl), low dose	1.41±0.39	1.56±0.48	1.55±0.46	1.52±0.61	1.70±0.59	0.51	0.29
Serum KIM-1 level (ng/dl), high dose	1.46±0.23	1.43±0.43	1.53±0.44	1.51±0.44	1.55±0.29		

Creatinine Clearance (Clcr) based on the Cockcroft gault formula [Clcr=(140-age)IBW÷72×Scr]

Urine Cys-C level neither changed significantly within nor between groups during vancomycin treatment. The same results were obtained for trend of serum KIM-1 changes (Table 2).

The mean±SD of serum vancomycin trough level before infusion of its 4th dose in the low and high dose groups were 8.07 ± 5.68 and 12.40 ± 9.20 mg/L, respectively. These values were 12.09± 10.16 and 15.92±11.11 mg/L in 10th day of treatment course. In 14 patients (36% versus 20% in high dose and conventional dose group respectively) achieved the target vancomycin trough level (>15 mg/L) before infusion of its 4th dose (p=0.04). The vancomycin trough level at 10th day of therapy in 12 (48%) patients in the high dose and 6 (24%) patients in low dose group was >15 mg/L. This difference was statistically significant (p=0.03).

Urine Cys-C level neither changed significantly within nor between groups (<15mg/L and ≥15 mg/L) during vancomycin treatment. Similar results were also observed for the trend of serum KIM-1 changes (Table 3).

Table 3. Comparing changes in serum Cystatin-C and KIM-1 and urine Cystatin-C during the study period in the patients with serum vancomycin trough level <15 mg/L and ≥15 mg/L.

Parameter/group	Baseline	Day 2	Day 4	Day6	Day 8	Between group P value	Within group P value
Serum Cystatin-C (mg/L)/ <15 mg/L	0.88±0.18	0.84±0.11	0.88±0.13	0.95±0.10	1.01±0.08	0.54	0.11
Serum Cystatin-C (mg/L)/ ≥15 mg/L	0.93±0.22	0.94±0.20	1.01±0.22	1.05±0.26	1.11±0.24		
Urine Cystatin-C (mg/L)/ <15 mg/L	0.03±0.04	0.04±0.03	0.05±0.02	0.05±0.04	0.06±0.04	0.45	0.19
Urine Cystatin-C (mg/L)/≥15 mg/L	0.04±0.01	0.05±0.02	0.05±0.00	0.06±0.01	0.07±0.02		
Serum KIM-1 level (ng/dl)/ <15 mg/L	1.40±0.38	1.50±0.54	1.54±0.22	1.55±0.60	1.57±0.56	0.16	0.55
Serum KIM-1 level (ng/dl)/≥15 mg/L	1.52±0.16	1.53±0.25	1.55±0.53	1.62±0.40	1.67±0.25		

Discussion

In this study, we try to compare vancomycin induced nephrotoxicity incidence between 15-20mg/kg BD & TDS based on the novel biomarkers of renal function (Cys-C and KIM-1) in patients with severe MRSA infections. In the current study, besides Scr, serum as well as urine level of Cys-C and serum KIM-1 level were measured at baseline and every other day until 8th day of vancomycin therapy. Although serum Cys-C level increased significantly during the treatment course, but there was no significant difference between conventional and high dose vancomycin groups. Serum Cys-C level began to rise at the second day of vancomycin therapy which was faster than Scr which detected at 6th day of the treatment course. Serum level of KIM-1 and urine Cys-C did not alter significantly during the treatment course in each group and also no significant difference between two groups was detected. Serum KIM-1 level began to rise at 6th day of vancomycin therapy simultaneously with Scr elevation and the elevation was relatively more considerable in high dose group. Urine Cys-C level alterations also followed the same pattern in our cohort.

Kidney injury is the major concern when vancomycin dose is optimized to reach high serum trough levels (≥15 mg/L) in severe bacterial infections (6). Following each unit elevation in serum vancomycin trough level, the risk of VIN increased 1.13 times (7).

In most of previous studies, serum creatitine was used as a marker of kidney injury and nephrotoxicity has been usually defined as a 0.5 mg/dL elevation in Scr if the initial Scr was ≤3 mg/dL, or a rise of >1 mg/dL if the initial Scr was >3 mg/dl (22-23). The incidence of VIN was reported 6-21% and up to 30% in patients received vancomycin for less than one week and more than 2 weeks, respectively and it occurs mostly 6-14 days after start of vancomycin administration (24-25). Incidence of VIN was reported 21% to 65% in vancomycin serum trough levels higher than 20 mg/L (26, 27). However, some experts believed that high vancomycin trough levels are the consequence of baseline renal insufficiency rather than being drug induced (6).

A common major limitation of previous studies in this field is evaluation of VIN based on the Scr alteration. Scr is an insensitive and non-specific marker of kidney injury which can be influenced by many non-renal factors such as sex, age, race, weight, muscle mass, and diet (28). Although Scr is freely filtered by the glomerulus, but it is reabsorbed and secreted to some extent by renal tubules which results in decreasing its accuracy as a marker of renal function. Moreover, large changes in renal function may be associated with the relatively small alterations in Scr in the first 24-48h following acute kidney injury (28). Recently novel and more sensitive biomarkers has been recommended for evaluation of renal function, detection of mild to moderate kidney dysfunction and determining the anatomic site of injury (6). Cys-C is a low molecular weight protein with positive charge which is freely filtered, reabsorbed and catabolized but not secreted by the tubules (17-18). Moreover, its serum and urine concentrations appear to be independent of sex, age, and muscle mass (29). Therefore Cys-C was introduced as a more sensitive marker of renal function than Scr in acute kidney injury. In addition, correlation between Clcr and serum Cys-C level was slightly higher than that for Scr (17-18, 29). Changes in these biomarkers' concentrations were significantly faster than Scr and BUN, specifically in the elderly populations (30).

KIM-1 is a tubular marker that is up-regulated in proximal tubules following ischemic and toxic injury (32). It was proposed as a highly sensitive and specific marker for detection of AKI and as gold index for detection of proximal tubule cells toxicity among 21 urinary markers (33).

Although urinary Cys-C concentration has been used in limited studies for evaluation of nephrotoxicity caused by different medications such as contrast media or chemotherapeutic agents, but in no clinical survey this marker was used for detecting vancomycin induced nephrotoxicity. Suzuki et al. studied serum Cys-C as a marker of kidney function in ICU patients and found a more remarkable correlation between Cys-C levels with Clcr than that with Scr (31). Although Cys-C is mostly reabsorbed from the proximal tubule cells due to its strong basic characteristic, but a measurable amount is still excreted in urine in correlation with urinary excretion of Cr which is non-absorbable from the tubular cells (15, 29). According to our findings, serum Cys-C appears to be a more sensitive marker than urine Cys-C and serum KIM-1 to detecting VIN. However, there was no significant difference in incidence of vancomycin induced nephrotoxicity between the groups. Also incidence of vancomycin induced nephrotoxicity was not significantly different between patients with vancomycin serum trough level <15mg/L and ≥15mg/L.

Small sample size, included patients with different type of infections, did not measure urine KIM-1 and short duration of follow-up are main limitations of our study. Designing a multicenter study with sufficient sample size in a subcategory of infection should be considered.

The findings showed that high dose vancomycin (15mg/kg every 8h) compared to low dose (15mg/kg every 12h) had comparable effects on the serum and urine biomarkers of kidney injury in patients with severe infections. Changes in the renal biomarkers of acute kidney injury during the first 8 days of vancomycin treatment were comparable between the low and high dose groups. Further studies on these biomarkers and also other novel markers are necessary for conclusive judgment.

Optimizing antibiotic dosing is essential to combat antimicrobial resistance. Renal safety is a major

concern when a high dose antibiotic with renal toxicity is considered to treat severe infections. Vancomycin as a key antibiotic for treatment of resistant gram positive infections is widely used in clinical practice. Several controversies are still exit regarding association between vancomycin trough level and its nephrotoxicity.

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