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ORIGINAL RESEARCH

Elevated Vancomycin Trough is Not Associated With Nephrotoxicity Among Inpatient Veterans

Kavitha K. Prabaker, MD[1,2], Thuong P.-H. Tran, PharmD[3,4], Tamara Pratummas, PharmD[3], Matthew Bidwell Goetz, MD[1,4,5], Christopher J. Graber, MD, MPH[1,4,5*]

[1]Department of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, California; [2]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California; [3]Pharmacy Service, VA Greater Los Angeles Healthcare System, Los Angeles, California; [4]Infectious Diseases Section, VA Greater Los Angeles Healthcare System, Los Angeles, California; [5]David Geffen School of Medicine, University of California, Los Angeles, California.

BACKGROUND: Vancomycin troughs of 15-20 mg/L are recommended in the treatment of invasive staphylococcal disease, higher levels than previously recommended.

OBJECTIVE/SETTING: We sought to determine if there was an association between vancomycin trough and nephrotoxicity, defined as 0.5 mg/L or 50% increase in serum creatinine, at a large Veterans Affairs medical center.

PATIENTS AND METHODS: We reviewed records of 348 inpatients at our institution who received ≥5 days of vancomycin during 2 time periods when vancomycin dosing protocols differed (May 2005-April 2006 and January 2007-December 2007). Potential risk factors for nephrotoxicity were collected prior to nephrotoxicity onset, and all patients with nephrotoxicity events occurring within 5 days of starting vancomycin were excluded.

RESULTS: Overall incidence of nephrotoxicity was 31/348 patients (8.9%). A similar percentage of patients experienced nephrotoxicity in 2005-2006 versus 2007 (16/201 vs 15/147, respectively; $P = 0.57$), despite a rise in mean (9.7 mg/L in 2005-2006 vs 13.2 mg/L in 2007; $P < 0.0001$) and highest (11.8 mg/L in 2005-2006 vs 15.7 mg/L in 2007; $P < 0.0001$) vancomycin trough levels achieved. In a multivariate logistic regression model, only receipt of intravenous contrast dye was significantly associated with nephrotoxicity (OR 4.01, $P < 0.001$), though there was a trend toward an association between maximum vancomycin trough ≥15 mg/L and nephrotoxicity (OR 2.05, $P = 0.082$). Overall reversibility of nephrotoxicity either prior to or within 72 hours of vancomycin discontinuation was 77.8%.

CONCLUSIONS: We conclude that nephrotoxicity, with higher trough levels occurring at ≥5 days of vancomycin therapy, was uncommon at our institution and typically reversible. *Journal of Hospital Medicine* 2012;7:91–97.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is responsible for an increasing number of invasive infections and, in the United States, may now be responsible for more deaths than disease associated with human immunodeficiency virus (HIV).[1,2] Vancomycin remains the drug of choice for invasive MRSA disease; from 1984 to 1996, its use in the United States escalated 6-fold.[3] With increased use of vancomycin, MRSA strains with partial and full resistance to vancomycin have emerged. Since 1997, *S. aureus* with intermediate susceptibility to vancomycin (VISA) as well as heteroresistance to vancomycin (hVISA) have been described.[4–6] Several centers have also noted a slow rise in minimum inhibitory concentration (MIC) among clinical MRSA isolates (''MIC creep'').[7] Low vancomycin trough levels have been implicated in the emergence of hVISA, and several studies have demonstrated a higher rate of vancomycin treatment failure, longer duration of fever, and prolonged hospitalization with hVISA and strains with elevated MIC compared to vancomycin-susceptible MRSA.[8–12] Until recently, vancomycin was frequently dosed to target trough levels <10 mg/L. The above concerns, combined with pharmacodynamic data suggesting that maintaining a ratio of vancomycin area under the curve to minimum inhibitory concentration (AUC/MIC) ≥400 may be associated with improved clinical outcome,[13] have prompted an expert consensus to recommend targeting higher vancomycin trough levels (typically 15-20 mg/L) for invasive MRSA infections and general avoidance of trough levels <10 mg/L.[14]

The effect of higher trough levels on kidney function remains poorly understood, as does the mechanism of vancomycin-induced renal injury itself, though animal

***Address for correspondence and reprint requests:** Christopher J. Graber, MD, MPH, Infectious Diseases Section, VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd, 111-F, Los Angeles, CA 90073; Tel.: 310-268-3015; E-mail: cgraber@ucla.edu

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studies demonstrate oxidative damage to renal tubules with high doses of vancomycin.[15,16] In previous studies, the incidence of vancomycin nephrotoxicity with lower troughs has been reported to range from 0% to 19% with vancomycin alone, increasing up to 35% with concomitant aminoglycoside therapy.[17–24] Limited studies have been done to assess the risk of nephrotoxicity at higher trough levels. Lodise and colleagues identified high-dose vancomycin (>4 gm per day) as an independent risk factor for nephrotoxicity, when compared to administration of <4 gm of vancomycin per day or use of linezolid, and showed greater risk of nephrotoxicity with increasing vancomycin trough levels within the first 96 hours of vancomycin administration.[25,26] Hidayat et al. demonstrated, in a prospective cohort analysis, that patients with mean trough levels ≥15 mg/L had a significantly increased incidence of nephrotoxicity. In that study, patients who developed nephrotoxicity were more likely to receive other nephrotoxic agents, and troughs collected before or after nephrotoxicity onset were not distinguished.[9] This is an important distinction, as vancomycin is frequently continued with dose adjustment even after nephrotoxicity occurs, with the nephrotoxicity resulting in subsequent higher troughs. Jeffres et al. demonstrated that maximum vancomycin trough ≥15 mg/L was associated with nephrotoxicity in patients with healthcare-associated MRSA pneumonia; this study was retrospective and focused on a particularly ill patient population.[27] Pritchard et al. also retrospectively reviewed 2493 courses of vancomycin at their institution, from 2003 to 2007, and found a significant relationship between vancomycin trough ≥14 mg/L and nephrotoxicity. The presence of comorbid disease states and concomitant nephrotoxins was determined in a subset of 130 courses in 2007; increasing vancomycin trough was associated with nephrotoxicity in multivariable analysis.[28] However, it is not clear whether troughs collected before or after nephrotoxicity onset were distinguished in this study. At least 6 other retrospective studies involving small sample size or published in abstract form have widely different results in relating high vancomycin trough or aggressive vancomycin dosing strategies to nephrotoxicity.[29–34]

The purpose of our study was to evaluate the association between development of nephrotoxicity and trough levels obtained during vancomycin therapy at a large veterans' hospital, while accounting for other potential nephrotoxins, and to evaluate the temporal association between elevated vancomycin troughs and nephrotoxicity. We chose to focus on nephrotoxicity that occurred on, or after, 5 days of vancomycin therapy in order to reduce other confounding factors of nephrotoxicity, since short durations of vancomycin frequently represent use in surgical prophylaxis or empirical therapy for hemodynamically unstable patients at high risk for renal injury.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

We performed a retrospective cohort study of patients at the Veterans Affairs (VA) Greater Los Angeles Healthcare System during 2 time periods (May 1, 2005-April 30, 2006 and Jan 1, 2007-Dec 31, 2007) when hospital guidelines recommended different vancomycin dosing regimens based on indication. During the first time period, the recommended target trough level was 10 mg/L, regardless of indication. In May 2006, target troughs were changed according to the following institutional guidelines: 8-12 mg/L for cellulitis, urinary tract infection (UTI), and uncomplicated bacteremia; 10-15 mg/L for endocarditis, osteomyelitis, and visceral abscesses; and 15-20 mg/L for bacterial meningitis and pneumonia. The vancomycin manufacturers (American Pharmaceutical Partners (Schaumburg, IL) and Baxter (Deerfield, IL)) were the same during both time periods. Patient data was collected from the VA Computerized Patient Records System (CPRS) by 2 trained reviewers (K.K.P. and T.P.). All inpatients who received ≥5 days of intravenous vancomycin therapy during these time periods were identified via electronic pharmacy records. We then excluded all patients with serum creatinine >2.0 mg/L prior to starting vancomycin, no serum creatinine collected before or during receipt of vancomycin, no trough levels drawn while on vancomycin (or for patients experiencing nephrotoxicity, no trough levels drawn prior to nephrotoxicity onset), nephrotoxicity occurring before day 5 of vancomycin therapy, and receipt of concomitant amphotericin B.

Data Collection and Study Definitions

In patients who received multiple courses of vancomycin during the specified time period, only the first course starting on, or after, May 1, 2005 and lasting ≥5 days was analyzed. Data collected for each patient included age, sex, race, and comorbidities (diabetes mellitus, liver dysfunction, and active malignancy). Diabetes mellitus was defined as 2 fasting blood glucose levels >125, or receipt of insulin or other hypoglycemic medications during vancomycin treatment. Patients were considered to have liver disease if they had a prior diagnosis of cirrhosis, hepatic encephalopathy, or hepatic insufficiency, or if 2 of the following criteria were met: total bilirubin >2 mg/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× the upper limit of normal, or serum albumin <3 g/dL. Receipt of ≥1 dose of potentially nephrotoxic agents, including aminoglycosides, intravenous furosemide, intravenous trimethoprim-sulfamethoxazole, intravenous contrast dye, potentially nephrotoxic chemotherapy, and vasopressors, were recorded beginning 72 hours prior to vancomycin therapy until onset of nephrotoxicity, or, if nephrotoxicity did not occur, the final vancomycin dose. Angiotensin-converting enzyme inhibitors (ACE-I) and

non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin were considered potentially nephrotoxic if they were newly started within 72 hours of vancomycin.

For each patient, the serum creatinine was recorded upon admission, within 24 hours of starting vancomycin, during vancomycin treatment, and at 24 hours and 72 hours following the final vancomycin dose. Serum creatinine was typically measured daily. Per institutional protocol, vancomycin trough levels were drawn 30-60 minutes prior to the fourth dose, and again in 5-7 days or with any large change in renal function. Extrapolated troughs were calculated by a pharmacist if levels were drawn outside of the 60-minute time period. The highest trough and duration of therapy was documented for each patient. The mean trough was equal to the arithmetic mean of all troughs obtained during vancomycin administration until 72 hours following the final dose.

Outcome Analysis

The primary end point was the development of nephrotoxicity, which was defined as an increase in serum creatinine by either $\geq$0.5 mg/dL or $\geq$50% for at least 2 consecutive days after receipt of vancomycin, up to 72 hours after the final dose, compared to the last creatinine measured prior to vancomycin initiation. Patients who had a documented isolated increase in serum creatinine that resolved upon recheck within 24 hours were not classified as experiencing nephrotoxicity. In patients who developed nephrotoxicity, mean troughs, maximum troughs, duration of vancomycin treatment, and receipt of concomitant nephrotoxins were ascertained using data collected only before nephrotoxicity onset. Bivariate and multivariate models were subsequently constructed in order to determine risk factors for nephrotoxicity, using either mean or maximum trough achieved prior to nephrotoxicity for each patient.

Statistical Methods

Comparisons between the 2005-2006 and 2007 groups were made using Student *t* test for continuous variables, Wilcoxon rank-sum test for ordinal variables, and Fisher's exact test for nominal variables. Association of clinical variables with nephrotoxicity was assessed using bivariate logistic regression with subsequent multivariable logistic regression. We initially decided to use maximum vancomycin trough $\geq$15 mg/L as the vancomycin exposure variable of interest to include in multivariable models, as we felt that (1) trough $\geq$15 mg/L is clinically relevant given current guidelines that recommend aiming for trough $\geq$15 mg/L for treatment of most invasive staphylococcal disease,[31] and (2) prior studies identified a single trough $\geq$15 mg/L as a possible risk factor for nephrotoxicity.[9,27,29,31] However, we also generated other multivariable models that included either maximum vancomycin trough $\geq$20 mg/L, mean vancomycin trough $\geq$15 mg/L, or mean vancomycin trough $\geq$20 mg/L, and models in which maximum and mean vancomycin troughs were treated as continuous variables. All variables were initially included in multivariable models; nonsignificant variables were removed from the models in a backwards stepwise fashion until likelihood ratio testing determined that removal of any variable was associated with likelihood ratio test *P* value <0.20 in comparing the full to reduced model. All calculated *P* values are two-sided. All calculations were performed with STATA, version 10 (StataCorp, College Station, TX). This study was approved via expedited review by the Institutional Review Board of the VA Greater Los Angeles Healthcare System.

RESULTS

Comparison of 2005-2006 Versus 2007 Cohorts

Of the 705 patients who were identified by pharmacy records to have received intravenous vancomycin, 348 patients remained after exclusion criteria were applied; the vast majority of patients were excluded because they received <5 days of vancomycin therapy. Of the 348 patients included in the study, 201 received vancomycin in 2005-2006, and 147 received vancomycin in 2007 (Table 1). Mean vancomycin trough was significantly higher in 2007 than 2005-2006 (average mean trough 13.2 mg/L $\pm$ 4.3 vs 9.7 mg/L $\pm$ 3.6; $P < 0.0001$), although median (8 vs 9 days) and mean (11.2 vs 12.2 days) duration of therapy was 1 day shorter in 2007 versus 2005-2006. Age, sex, race, comorbidities, and indication for vancomycin use were similar between the 2 groups. The receipt of concomitant nephrotoxins was largely similar between the 2 time periods, with the primary exception being that a higher proportion of patients received intravenous contrast dye in 2007 (19%) than in 2005-2006 (8.0%) ($P = 0.003$), and a lower proportion of patients received amikacin in 2007 (7.5%) than in 2005-2006 (15%) ($P = 0.043$), though overall receipt of aminoglycosides was similar. Overall, nephrotoxicity was noted in 31 patients (8.9%), with similar incidence in 2005-2006 (8.0%) and 2007 (10.2%) ($P = 0.57$). The median time to onset of nephrotoxicity was 7 days, with a median peak serum creatinine of 1.8 mg/dL.

Determination of Clinical Factors for Nephrotoxicity

Results of bivariate and multivariate analysis of clinical factors potentially associated with nephrotoxicity are displayed in Table 2. Among the 31 patients experiencing nephrotoxicity, the mean maximum vancomycin trough prior to nephrotoxicity onset was 14.9 mg/L, compared to 13.3 mg/L among those not experiencing nephrotoxicity (OR 1.03 for each 1 mg/L increment in mean trough, 95% confidence interval [CI] 0.98-1.09; $P = 0.21$). While there was a trend toward patients with nephrotoxicity having a maximum trough $\geq$15 mg/L, it was not significant in either bivariate (OR 2.18, 95% CI 0.85-5.63; $P = 0.11$) or

TABLE 1. Characteristics of Patients Treated With Vancomycin From May 2005 Through April 2006 and From January to December 2007

	2005-2006 (n = 201)	2007 (n = 147)	*P* Value*	Combined (n = 348)
Patient characteristics				
Age (median years)	59	61	0.18	60
Male gender (no. of patients)	198 (99%)	141 (96%)	0.18	339 (97.4%)
Race (no. of patients):				
White	128 (63.7%)	95 (64.6%)	0.91	223 (64.1%)
Black	57 (28.4%)	40 (27.2%)	0.90	97 (27.9%)
Other race	16 (8%)	12 (8.2%)	1.00	28 (8%)
Comorbidities (no. of patients):				
Diabetes	75 (37.3%)	50 (34%)	0.57	125 (35.9%)
Liver disease	29 (14.4%)	14 (9.5%)	0.19	43 (12.4%)
Malignancy	33 (16.4%)	21 (14.3%)	0.65	54 (15.5%)
Concomitant nephrotoxins (no. of patients):				
Aminoglycosides (any):	41 (20.4%)	25 (17.0%)	0.49	66 (19.0%)
Gentamicin	11 (5.5%)	14 (9.5%)	0.21	25 (7.2%)
Amikacin	30 (14.9%)	11 (7.5%)	0.043	41 (11.8%)
IV Furosemide	53 (26.4%)	34 (23.1%)	0.53	87 (25.0%)
ACE-inhibitor (newly started)	20 (10%)	10 (6.8%)	0.34	30 (8.6%)
NSAID (newly started)	26 (12.9%)	11 (7.5%)	0.12	37 (10.6%)
IV Trimethoprim-sulfamethoxazole	3 (1.5%)	2 (1.4%)	1.00	5 (1.4%)
Contrast dye	16 (8%)	28 (19.0%)	0.003	44 (12.6%)
Chemotherapy	3 (1.5%)	4 (2.7%)	0.42	7 (2%)
Vasopressors (any):	13 (6.5%)	7 (4.8%)	0.64	20 (5.7%)
Dopamine	4 (2%)	1 (0.7%)	0.40	5 (1.4%)
Epinephrine	5 (2.5%)	1 (0.7%)	0.41	6 (1.7%)
Norepinephrine	9 (4.5%)	5 (3.4%)	0.78	14 (4.0%)
Phenylephrine	2 (1.0%)	1 (0.7%)	1.00	3 (0.9%)
Vasopressin	0 (0%)	1 (0.7%)	0.42	1 (0.3%)
Indication for vancomycin:				
Skin/soft tissue/bone infection	112 (55.7%)	77 (52.4%)	0.59	189 (54.3%)
Pneumonia	26 (12.9%)	26 (17.7%)	0.23	52 (14.9%)
Bacteremia	26 (12.9%)	14 (9.5%)	0.40	40 (11.5%)
Other†	37 (18.4%)	30 (20.4%)	0.68	67 (19.3%)
Clinical outcomes				
Nephrotoxicity (no. of patients)	16 (8%)	15 (10.2%)	0.57	31 (8.9%)
Mean admission creatinine (mg/L)	1.10	1.16	0.25	1.13
Mean vancomycin trough (mg/L)	9.71	13.2	<0.0001	11.2
Mean highest vancomycin trough (mg/L)	11.8	15.7	<0.0001	13.5
Vancomycin duration (median days)	9	8	0.014	8

Abbreviations: ACE, angiotensin-converting enzyme; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug. *Comparison of continuous variables done by Student *t* test, ordinal variables by Wilcoxon rank-sum test, and nominal variables by Fisher's exact test. †Osteomyelitis, urinary tract infection, endocarditis, meningitis, otomastoiditis, empiric therapy.

multivariate (OR 2.05, 95% CI 0.91-4.61; $P = 0.082$) analysis. The duration of vancomycin therapy was also not significantly associated with nephrotoxicity, both when evaluated as a continuous variable and when prolonged courses ($\geq$14 days) were compared to short courses (between 5 and 14 days) of therapy. Other multivariable models were constructed that included maximum trough $\geq$20 mg/L, mean trough $\geq$15 mg/L, mean trough $\geq$20 mg/L, and maximum and mean trough as continuous variables; in all of these models, the vancomycin exposure variable of interest was not significant enough to remain in the final model after backwards elimination. The only factor significantly associated with nephrotoxicity in either bivariate or multivariate analysis was receipt of intravenous contrast dye (OR 3.64, 95% CI 1.52-8.68; $P = 0.004$ in multivariate analysis).

Reversibility of Nephrotoxicity

Of the 31 patients with nephrotoxicity, 20 (64.5%) patients still met criteria for nephrotoxicity at the time of vancomycin discontinuation. Nephrotoxicity subsequently resolved in 10 of the 16 patients that were still nephrotoxic at the time of vancomycin discontinuation (4 patients did not have follow-up creatinine checked within 72 hours of vancomycin discontinuation). Thus, overall reversibility of nephrotoxicity either prior to, or within, 72 hours of vancomycin discontinuation was 77.8% (21/27 patients). Of the 6 patients who remained persistently nephrotoxic at 72 hours, all had received concomitant nephrotoxins prior to the onset of nephrotoxicity, as compared to 15/21 (71.4%) patients whose nephrotoxicity resolved ($P = 0.28$ by Fisher's exact test). Only 1 persistently nephrotoxic patient required dialysis: a critically ill

TABLE 2. Association of Clinical Factors With Nephrotoxicity

			Bivariate Analysis		Multivariate Analysis	
Clinical Factor	NT (n = 31)	No NT (n = 317)	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Patient demographics						
Age (median)	64 yr	60 yr	1.01	0.48		
Male sex	31	308	N/A	1.00		
Race:						
White	17	206	1.0 (reference)	...		
Black	10	87	1.39	0.43		
Other	4	24	2.02	0.24		
Vancomycin characteristics						
Mean trough (mg/L), mean per group:	12.1	11.1	1.05*	0.19		
Patients with mean trough <10 mg/L	9	140	1.0 (reference)	...		
Patients with mean trough 10-15 mg/L	15	130	1.79	0.18		
Patients with mean trough ≥15 mg/L	7	47	2.32	0.11		
Highest trough (mg/L), mean per group	14.9	13.3	1.03*	0.21		
Patients with highest trough <10 mg/L	7	107	1.0 (reference)	...		
Patients with highest trough 10-15 mg/L	10	112	1.36	0.54		
Patients with highest trough ≥15 mg/L	14	98	2.18	0.11	2.05	0.082
Days of vancomycin therapy (median)	7	8	0.97†	0.40	0.96	0.17
≥14 days of vancomycin therapy	7	71	1.01	0.98		
Clinical characteristics						
SCr >1 mg/L prior to vancomycin	11	136	0.73	0.43		
Diabetes	10	115	0.84	0.66		
Liver disease	3	40	0.74	0.64		
Malignancy	5	49	1.05	0.92		
Concomitant nephrotoxins (any):	21	174	1.73	0.17		
Aminoglycosides (any):	7	59	1.28	0.59		
Amikacin	3	38	0.79	0.70		
Gentamicin	4	21	2.09	0.21		
Furosemide (intravenous)	10	77	1.48	0.33		
ACE-inhibitor (newly started)	1	29	0.33	0.29	0.31	0.27
NSAIDs (newly started)	2	35	0.56	0.44		
TMP-SMX (intravenous)	2	3	7.22	0.034		
Contrast dye (intravenous)	10	34	3.96	0.001	4.01	0.001
Chemotherapy	1	6	1.73	0.62		
Vasopressors (any):	1	19	0.52	0.53		
Dopamine	0	5	0	1.0		
Epinephrine	0	6	0	1.0		
Norepinephrine	1	13	0.78	0.81		
Phenylephrine	0	3	0	1.0		
Vasopressin	0	1	0	1.0		

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug; NT, nephrotoxicity; TMP-SMX, trimethoprim-sulfamethoxazole; SCr, serum creatinine. *Odds ratio per 1 mg/L increase in trough level. †Odds ratio per 1 additional day of vancomycin therapy.

patient with multiorgan failure for whom care was withdrawn within 4 days of vancomycin discontinuation.

DISCUSSION

Over the past 5 years, many institutions have adopted higher dosing guidelines for vancomycin, based on pharmacokinetic concerns related to its performance in the treatment of invasive staphylococcal disease. The data on nephrotoxicity at these higher troughs are limited. Previous studies that address the relationship between higher vancomycin troughs and nephrotoxicity suffer from small sample size[29,33]; do not address reversibility of nephrotoxicity[9,26,29–31,33]; may not account for the temporal relationship between the development of nephrotoxicity and high trough levels,[9,28–31] or examine patient populations at relatively high[27] or low[30] risk for renal injury apart from receipt of vancomycin. A recent expert consensus statement identified these factors as limiting the strength of evidence for a direct causal relationship between elevated vancomycin troughs and nephrotoxicity.[14] A recent review by Hazlewood et al. concluded that the incidence of nephrotoxicity remains low in patients without preexisting renal disease and those not receiving concomitant nephrotoxins.[35] The aim of our study was to identify whether or not there was a correlation between high-dose vancomycin and nephrotoxicity, while accounting for their temporal relationship, concomitant nephrotoxin use, and reversibility. In particular, we chose to focus on nephrotoxicity occurring after at least 5 days of vancomycin

therapy in order to reduce confounding by other possible sources of renal injury that may have affected the decision to initially prescribe vancomycin, an approach advocated by a recent review.[36] While we noted that mean and maximum vancomycin troughs were significantly higher in 2007 than 2005-2006, incidence of nephrotoxicity was stable between the 2 time periods, with the higher rate of intravenous contrast dye in 2007 balanced in part by less aminoglycoside use. Overall, higher trough levels were not necessarily accompanied by a significant increase in nephrotoxicity, though there was a nonsignificant trend toward more nephrotoxic patients having maximum trough $\geq$15 mg/L.

The only clinical factor that was significantly associated with nephrotoxicity in multivariate analysis was receipt of intravenous contrast dye. Of the 44 patients who received intravenous contrast dye, 10 (22.7%) experienced nephrotoxicity. Interestingly, in animal studies, both intravenous contrast dye[37,38] and high-dose vancomycin[15,16] have been demonstrated to promote free radical formation within renal tissue, which is hypothesized to cause tubular damage primarily through vascular endothelial dysfunction, vasoconstriction, and subsequent reperfusion injury. N-acetylcysteine is frequently administered to patients about to receive intravenous contrast dye (although its benefit remains controversial[37,39]); N-acetylcysteine has also been shown in an animal model to attenuate vancomycin-induced renal injury.[40]

Receipt of concomitant aminoglycosides was not significantly associated with nephrotoxicity, in contrast with previous studies. One meta-analysis of 8 studies revealed found that the incidence of nephrotoxicity associated with combination vancomycin and aminoglycosides was 13.3% greater than with vancomycin alone ($P < 0.01$) and 4.3% greater than therapy with an aminoglycoside alone ($P < 0.05$)[20]; another analysis of safety data of the clinical trial comparing daptomycin to comparator therapy including initial low-dose gentamicin therapy in the treatment of *S. aureus* bacteremia found renal adverse events in 10 of 53 (19%) patients receiving vancomycin and gentamicin, compared to 8 of 120 (7%) patients receiving daptomycin.[41] While our findings that show no clear relationship between concomitant vancomycin and aminoglycoside use and nephrotoxicity may have been due to the relatively small number of patients in our study who received aminoglycosides, it is worth noting that more patients in our study received aminoglycosides than intravenous contrast dye (66 vs 44 patients). The 77.8% overall resolution of nephrotoxicity observed in our study is similar to that reported by Farber and Moellering in 1983[19] and to that reported more recently with high-dose vancomycin by Jeffres et al. and Teng et al.[27,34]

Although we attempted to account for as many confounders as possible, the retrospective nature of our study prevents us from making definitive statements regarding the role of vancomycin trough levels and nephrotoxicity. In particular, we are unable to comment on any potential role vancomycin may have on nephrotoxicity within 5 days of its start or on patients with a baseline serum creatinine >2. Other significant limitations include our small proportion of female patients, and that we were not able to calculate severity of illness or determine the presence of congestive heart failure. Also, we may be dosing vancomycin less aggressively than other centers, and thus may have reduced power in determining whether higher troughs, particularly those $\geq$20 mg/L, are associated with nephrotoxicity; identification of more patients with higher troughs and a larger overall sample size may have yielded different results. Even in the 2007 group, a significant number of patients with cellulitis, UTI, and uncomplicated bacteremia had target troughs of 8-12 mg/L. However, taken together, our findings do not support a definite relationship between vancomycin troughs and development of nephrotoxicity, and that when it does occur, it is largely reversible. Further prospective research is needed to evaluate the effects of aggressive vancomycin dosing regimens on nephrotoxicity, particularly those regimens that include large loading doses. Trials of antioxidative agents in patients receiving aggressive dosing regimens of vancomycin who require radiology studies involving intravenous contrast dye may be indicated as well.

Kavitha K. Prabaker's current affiliation is Department of Medicine, Rush University Medical Center, Chicago, Illinois.

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