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Applying New Diagnostic Criteria for Acute Kidney Injury To Facilitate Early Identification of Nephrotoxicity in Vancomycin-Treated Patients▽

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Acute kidney injury (AKI) associated with high-dose vancomycin (VAN) therapy is a clinical concern, but no uniform diagnostic criteria exist. The AKI Network (AKIN) proposed new criteria to diagnose AKI based on abrupt changes in serum creatinine or urine output. We conducted a prospective observational study to determine the incidence and severity of AKI and associated outcomes using the AKIN criteria versus traditional definitions. Eligible patients ($n = 227$) were elderly (median, 70 years) and received VAN therapy for 8 days (median). AKI occurred in 43 patients (19%) using AKIN criteria at an onset of 6 days. AKI incidence was similar for patients with a trough level of ≥15 (24%; 17/72) versus <15 (17%; 26/155) μg/ml. Compared to non-AKI patients, more AKI patients resided in the intensive care unit (ICU) (47% [20/43] versus 27% [50/184]; $P = 0.017$), had a prior AKI episode (19% [8/43] versus 7% [5/184]; $P = 0.001$), and received vasopressor (28% [12/43] versus 14% [25/184]; $P = 0.04$) and/or nephrotoxins (84% [36/43] versus 67% [123/184]; $P = 0.04$). Seventeen of the AKI patients met traditional criteria, of whom more patients had stage 2 and 3 AKI (76% versus 8%; $P = 0.0001$), dosage adjustment (41% versus 15%) and renal consultation (35% versus 12%), prolonged length of stay after AKI (11 versus 7.5 days) and died (29% versus 12%) than those diagnosed by AKIN criteria (*P* value not significant). Use of AKIN criteria for AKI has the potential to improve care of VAN-treated patients by facilitating early detection of AKI and warrants confirmation in large prospective trials.

Acute kidney injury (AKI) has been defined as an abrupt change in kidney function often secondary to an injury that causes functional or structural changes in the kidneys (1). AKI complicates up to 7% of all hospital admissions and 25% of intensive care unit (ICU) admissions (13). While progress has been made in understanding the pathophysiology of AKI and in the clinical care of patients with AKI, mortality rates have remained unchanged at 50 to 70% over the past 50 years. Among survivors of AKI who required acute renal replacement therapy, 41% persisted with renal insufficiency while 50% died at 5 years postdischarge.

One of the significant barriers to improvement in clinical outcomes has been the lack of a standard definition and staging of AKI. In recent years both the Acute Dialysis Quality Initiative (ADQI) group and the Acute Kidney Injury Network (AKIN) published diagnostic criteria for AKI. The ADQI definition is based on the risk–injury–failure–loss–end-stage renal disease (RIFLE) classification scheme (1). Risk is defined by an increase in serum creatinine (Scr) of ≥50% or a reduction in urine output (UOP) to <0.5 ml/h/kg of body weight for 6 h. Studies have shown that the worse the RIFLE class, the higher the mortality rate, the longer the ICU stay and hospital stay, and the lower the renal recovery rate will be (3).

Similarly, the AKIN proposed new diagnostic criteria, defined as an abrupt (within 48 h) reduction in kidney function signified by an absolute increase in Scr of ≥0.3 mg/dl (or ≥26.4 μmol/liter), an increase in Scr of ≥50% (1.5-fold from the baseline level), or a reduction in urine output (documented oliguria of <0.5 ml/kg/h for >6 h) (9). Drug-induced nephrotoxicity accounts for up to one-third of in-hospital AKI cases (13). Traditionally, drug-induced nephrotoxicity (NT) has been defined in the published literature as an increase of ≥0.5 mg/dl (or a 50% increase) in Scr over the baseline level or a decrease in creatinine clearance (CrCL) of ≥50% from baseline on two consecutive days in the absence of an alternative explanation. A potential advantage in using the AKIN diagnostic criteria in particular is that patients at risk for drug-induced acute kidney injury may be identified early, allowing prompt interventions prior to the development of renal failure.

Nephrotoxicity has become increasingly reported with use of high-dose intravenous (i.v.) vancomycin (VAN) therapy, particularly when the drug is prescribed for a prolonged duration in those receiving concomitant nephrotoxins (14). Studies have suggested oxidative stress and mitochondrial damage to be involved in the pathogenesis of toxicity (4). Although nephrotoxicity from VAN monotherapy has been shown to be reversible at typical doses (5), AKI can further complicate a patient's hospital course, with a greater rate of long-term mortality and other adverse outcomes than for patients who survive hospitalization without AKI (2). In order to limit the patient's risk of AKI secondary to high-dose VAN therapy and facilitate prompt intervention, a new VAN dosing protocol has been implemented at our institution to include use of the new AKI diagnostic criteria to monitor for drug-induced kidney injury. The protocol calls for reassessment of VAN dosing or consid-

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eration of alternative therapies if the patient experiences abrupt changes in renal function, UOP or an acute change of ≥0.3 mg/dl in Scr within 48 h. Previous studies on VAN-associated nephrotoxicity have used the NT definition and not the AKIN definition.

The objectives of this study were to determine the incidence of AKI, predisposing risk factors, and the impact of AKI on outcomes for hospitalized patients receiving VAN therapy using AKIN criteria. Our secondary objective was to use both AKIN and RIFLE criteria to stage the severity of renal injury in those who developed AKI.

MATERIALS AND METHODS

This was a prospective observational study conducted from November 2009 to June 2010 at a 525-bed community teaching hospital in Pasadena, CA. Study patients were screened from a biweekly antibiotic report generated from the Meditech system. Patients were eligible for the study if they met the following criteria: age of >17 years, ≥5 days of VAN therapy, and ≥1 VAN trough level drawn. Patients were excluded from the study if they had a Scr level of ≥2 mg/dl at admission or had a past medical history of chronic kidney disease (CKD) at stage III or worse. Medical and laboratory records of eligible patients were reviewed for pertinent demographic, laboratory, and clinical information: age, residence prior to admission, diagnosis upon admission, baseline comorbidities, indication for VAN therapy, concomitant medications known to affect kidney function (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme (ACE) inhibitors, loop diuretics, i.v. contrast, aminoglycoside antibiotics, and vasopressors), hydration status, length of hospital and ICU stay, Scr level at baseline, peak, and discharge, blood urea nitrogen (BUN), urine output, VAN trough levels, duration of VAN treatment, positive microbiology results, antibiotic therapy besides VAN, and in AKI patients, need for renal replacement therapy, renal consultation, and dosage adjustment of other drugs. The data were recorded on a structured data collection form and entered into a relational database (Microsoft Access). The lowest known Scr value prior to admission was recorded as the baseline Scr value; otherwise, the lowest Scr value between the time of admission and the period prior to VAN therapy was recorded as the baseline value. Baseline renal function was estimated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-epi) equations to calculate the glomerular filtration rate (GFR) (12). The average VAN trough concentration was calculated by the following equation: [(trough 1 × no. of days with trough 1) + (trough 2 × no. of days with trough 2) + (trough n × no. of days with trough n)]/total no. of days on VAN therapy (6). Of note, each vancomycin trough concentration was assessed whether it was obtained at the appropriate times; any that were measured prior to steady state or at the wrong times were not used in the average trough calculation. Depending on the clinical status of the patient, it is at the discretion of the clinical pharmacist whether a trough concentration is checked prior to reaching steady state. Severity of kidney injury in patients who developed AKI was staged according to the RIFLE and AKIN criteria.

The VAN dosing protocol includes a loading dose and maintenance dose. The loading dose equation is volume of distribution (V) × peak concentration (C_{pk}), with a target C_{pk} of 25 to 30 μg/ml. The maintenance dose calculation is based on the trough concentration × V × $(1 - e^{-kT})/e^{-kT}$, with T as the dosing interval. The dose varies by the target trough concentration. Recommended trough concentrations per protocol were 15 to 20 μg/ml for organisms with documented MICs of ≥1.0 μg/ml and for the treatment of pneumonia, bacteremia, meningitis, osteomyelitis, or endocarditis regardless of MIC and 10 to 15 μg/ml for all other types of infections.

For our primary analysis, the AKIN definition was used to identify VAN-induced AKI in patients receiving at least 5 days of VAN therapy where no alternative explanation for AKI was identified. Patients with abrupt increases in Scr due to changes in fluid balance (i.e., dehydration) were excluded from the analysis. Dehydration was suspected if there was a rapid decline in the patient's weight or if Scr and BUN normalized within 48 h following administration of fluids.

Risk factors for development of AKI during VAN therapy and the impact of AKI on outcomes were compared between patients who developed AKI and those who did not. Risk factors included age, baseline renal function, acute physiology and chronic health evaluation II (APACHE II) score, comorbid conditions, ICU admission, concomitant exposure to other nephrotoxins, and duration and exposure of VAN. Outcome measures included severity and reversibility of AKI, length of hospital stay, and 28-day mortality. Of note, length of stay was assessed only for patients who were discharged alive from the hospital. Additionally, for our secondary analysis, patients were screened for AKI using the traditional definition of NT, defined as an increase of ≥0.5 mg/dl (or a 50% increase) in Scr over baseline levels in consecutively obtained daily Scr values or a drop in calculated CrCL of ≥50% from baseline on two consecutive days in the absence of an alternative explanation. Patients diagnosed with AKI based on AKIN standards were also compared to those diagnosed based on commonly used criteria (NT) to assess the impact of new diagnostic criteria on the incidence of VAN-induced AKI, degree of injury at the time of diagnosis, and process of care, such as the need for nephrology consultations or dosage adjustment for other medications.

The study was approved by the Institutional Review Board at Huntington Hospital. Patient consent was not obtained for this prospective observational study since no interventions were made by the study investigators that may have affected patient care. All vancomycin trough measurements were performed as part of routine care of the patient and not for the purpose of this study.

Statistical analysis. Chi-square or Fisher's exact test was performed for all categorical variables, and the Student t test was performed for all continuous variables. We performed univariate analysis of each variable by fitting a univariate logistic regression model to determine the effect of each predictor variable for development of AKI. Multiple logistic regression models were then fitted using variables with a P value of <0.25 from the univariate models to identify the independent risk factors, including relevant variables controlled as covariates. A stepwise model selection method was employed.

A P value of <0.05 denotes significance. Statistical analysis was performed using the GraphPad Prism v4.0 (San Diego, CA) and SAS v9.2 (Carly, NC) software programs.

RESULTS

A total of 855 adult patients hospitalized between November 2009 and June 2010 and who received intravenous VAN were screened. A total of 628 patients were excluded from the study for the following reasons: 546 patients received VAN for <5 days, 43 patients were dialysis dependent or had end-stage renal disease prior to admission, 14 patients had Scr of >2 mg/dl or CKD stage III or higher, three patients did not have available labs, and four patients did not have VAN trough levels drawn. Eighteen patients had abrupt changes in Scr and BUN that promptly returned to baseline following i.v. hydration; thus, those patients were excluded from the analysis since the change in Scr values was felt to be due to dehydration and not related to VAN.

Two hundred twenty-seven patients met inclusion criteria and were evaluated. AKI according to the AKIN definition developed in 19% (43/227) of patients; the remaining 184 patients did not develop AKI and were included in the non-AKI group. The study cohort was comprised of an elderly population with a median age of 70 years. Baseline characteristics were similar in the two groups, except that the AKI group had a significantly lower baseline GFR according to both the MDRD and CKD-epi equations, higher APACHE II scores within 24 h of admission, and more patients with a history of malignancy (Table 1).

The mean onset of AKI was 6 ± 2.6 days, and the median duration of VAN therapy was 9 days in the AKI group. The initial daily dose was 27 mg/kg in the non-AKI group, compared to 23 mg/kg in the AKI group. Nearly all patients in the non-AKI group, 99% (182/184), and the AKI group, 98% (42/43), had VAN therapy dosed and monitored by clinical pharmacists. The indication for VAN therapy was empirical for 74% (168/227) of patients overall; however, once culture reports were available, only 26% (59/227) of patients remained on VAN as directed therapy. Trough levels were drawn more

TABLE 1. Baseline characteristics

Characteristic	Value(s) for group[c]	
	Non-AKI	AKI
Demographics		
Age, yr (median, IQR[a])	70 (56, 81)	68 (58, 84)
Male	89 (49)	26 (61)
Weight, kg (median, IQR)	68 (59, 83)	75 (63, 86)
APACHE II score (median, IQR)	8 (6, 13)	9 (8, 15)
Baseline estimated GFR (median, IQR)		
MDRD (ml/min/1.73 m^2)	118 (92, 152)*	102 (67, 122)*
CKD-epi (ml/min/1.73 m^2)	99 (83, 112)*	87 (67, 107)*
ICU admission	56 (30)	18 (42)
Residence prior to admission		
Home	125 (68)	32 (74)
SNF	59 (32)	11 (26)
Comorbidities		
Diabetes	52 (28)	16 (37)
Cardiovascular disease[b]	114 (62)	27 (63)
Renal insufficiency	6 (3)	2 (5)
Chronic obstructive pulmonary disease	26 (14)	4 (9)
Malignancy	28 (15)[Y]	16 (37)[Y]

[a] IQR, interquartile range.
[b] Congestive heart failure, atrial fibrillation, hypertension.
[c] Where not otherwise noted, a value is the no. (%) of patients with the given characteristic. *, P value < 0.05, Wilcoxon-Mann-Whitney test; Y, P value < 0.05, chi-square test. For non-AKI group, $n = 184$; for AKI group, $n = 43$.

often in the AKI group than in the non-AKI group (median, 3 versus 2; $P = 0.004$).

Risk factors. When the two groups (AKI versus non-AKI patients) were compared for risk factors predisposing to the development of AKI, a significantly greater proportion of patients in the AKI group were exposed to vasopressors during their hospital admission (28% [12/43] versus 14% [25/184]; $P = 0.02$). In addition, a significantly greater proportion of patients in the AKI group than non-AKI patients received nephrotoxic agents during VAN therapy (84% [36/43] versus 67% [123/184]; $P = 0.03$). Nephrotoxic agents included i.v. contrast, aminoglycosides, NSAIDs, loops diuretics, and ACE inhibitors. AKI patients were exposed to nephrotoxic agents concurrently with VAN for a median of 3 days. AKI developed in 6 of 58 (10%) patients who did not receive vasopressors or nephrotoxic agents concurrently with VAN therapy (Fig. 1). The incidence of AKI in patients who received any vasopressor or nephrotoxic agent concurrently with VAN was 22% (37/169). More patients in the AKI group also had a prior episode of AKI (19% [8/43] versus 3% [5/184]; $P = 0.0006$). Prior episodes of AKI were noted from patients' previous admissions as documented in physician progress notes or if the patient's Scr level changed in accordance with the AKIN criteria. Vancomycin was the cause of the prior episode of AKI in 14% of patients. Neither the proportion of patients attaining an average trough level of ≥15 μg/ml (40% AKI [17/43] versus 30% [55/184] non-AKI patients; P value not significant [ns]) nor the duration of VAN exposure differed between the two groups. Nearly half (47%) of non-AKI patients and 63% of AKI patients received VAN for greater than 7 days (P value ns).

Risk factors significant for the development of AKI from univariate analysis were included in the multivariate regression model as covariates (Table 2). The strongest predictor for the development of AKI in patients receiving VAN therapy included a prior episode of AKI, a history of malignancy, concurrent ICU stay, and baseline GFR estimated by the CKD-epi equation in descending order of significance. Age, average VAN trough level of ≥15 μg/ml, concurrent nephrotoxic therapy, or prolonged VAN exposure (>7 days) were not significant predictors. Of note, we have modeled VAN trough concentration as above and below 20 μg/ml and as a continuous variable; P values in both cases remain insignificant in the multivariate analysis ($P = 0.8075$ and 0.3026, respectively) to identify risk factors predictive of AKI development.

Outcomes. Nearly half (44%) of AKI patients had Scr values that remained above baseline by the time of discharge or death. More importantly, development of AKI was significantly associated with a higher rate of death (19% versus 5%; $P < 0.05$), a longer total length of hospital stay (15 days versus 11 days; $P < 0.05$), and a longer duration of hospital stay after initiation of VAN therapy (13 days versus 9 days; $P < 0.05$) (Table 3).

AKIN versus NT. The incidence of AKI was higher using the AKIN definition than using the NT definition, 19% (43/227) versus 7% (17/227), respectively (Table 4). Specifically, the AKIN criteria for AKI captured more patients in earlier stages of injury according to both AKIN and RIFLE staging schemes than did NT criteria. Most (92%) patients with AKI diagnosed by the AKIN criteria had stage 1 kidney injury by AKIN staging, while the majority (59%) of the patients with AKI diagnosed by NT criteria were in stage 2. Similarly, when RIFLE staging criteria were used, 65% of AKIN-diagnosed patients were in the "risk" stage while 65% of NT patients were in the "injury" stage.

Despite the similar number of patients diagnosed by AKIN and NT with Scr values remaining above baseline at the time of discharge or death, a trend toward higher mortality (29% versus 12%; P = ns) and longer length of stay after AKI (median

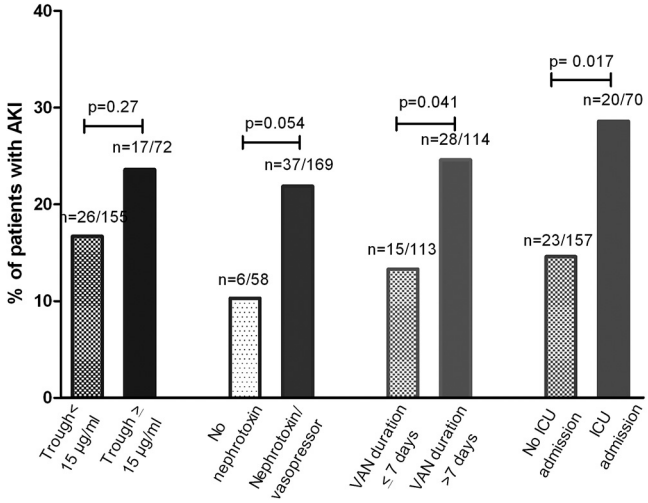

FIG. 1. Incidence of acute kidney injury. Fisher's exact test was calculated for all comparisons.

TABLE 2. Univariate and multivariate regression analysis of risk factors for developing AKI

Variable	Univariate analysis OR (CI)	Multivariate regression analysis	*P* value
Age	1.007 (0.987–1.027)	0.981 (0.952–1.011)	0.2
Baseline CrCl (MDRD)	0.989 (0.980–0.997)*		
Baseline CrCl (CKD-epi)	0.978 (0.964–0.993)*	0.972 (0.951–0.993)*	0.0082
APACHE II	1.045 (0.991–1.102)		
Malignancy	2.690 (1.265–5.717)*	2.745 (1.189–6.339)*	0.018
Prior episode of AKI	8.183 (2.528–26.487)*	6.311 (1.621–24.565)*	0.0079
Current VAN exposure > 7 days	1.881 (0.951–3.724)	1.722 (0.785–3.777)	0.18
Concurrent ICU stay	2.313 (1.170–4.574)*	2.497 (1.158–5.385)*	0.02
Vasopressor exposure**	2.462 (1.119–5.417)*		
No. of days vasopressor given concurrently**	1.273 (0.992–1.634)		
No. of nephrotoxic agents given concurrently	2.550 (1.073–6.062)*		
Duration of VAN therapy (days)	1.051 (0.967–1.142)		
Average trough ≥ 15 μg/ml	1.495 (0.752–2.972)	1.128 (0.510–2.492)	0.77

OR, odds ratio; CI, 95% confidence interval.
*, *P* value < 0.05; **, *n* = 37, too small to include this variable in the multivariate model.

11 versus 7.5 days; *P* value ns) was observed in the NT group compared to results for the AKIN group. None of the AKI patients progressed to acute renal failure that required renal replacement therapy. VAN was discontinued after AKI in 23% of patients in the AKIN group and 47% in the NT group. Similarly, other interventions (e.g., dosage adjustment of other concomitant medications, nephrologist consultations, and pharmacist interventions for monitoring of patients for renal dysfunction (*P* value ns) were needed more frequently in the NT group; however, the difference did not reach statistical significance.

DISCUSSION

Nephrotoxicity has traditionally been defined as a larger change in Scr than that defined by AKIN criteria (0.5 versus 0.3 mg/dl). However, recent studies have shown that even a small increase in Scr is associated with negative outcomes. The AKIN criteria were developed in order to identify rapid but clinically significant changes in Scr in order to make appropriate interventions prior to a patient progressing on to renal failure. The incidence of VAN-associated AKI at our institution was 19% according to the AKIN criteria. To the best of our knowledge, this is the first study utilizing the AKIN criteria to define AKI in a hospitalized adult population receiving VAN therapy, regardless of their acuity. Hutschala et al. used the AKIN criteria to compare the incidence of AKI associated with continuous infusion versus intermittent administration of VAN in a retrospective cohort of ICU patients following open-heart surgery (7). The incidence of AKI in their study was

TABLE 3. Impact of AKI on outcomes

Variable	Value for group[a]	
	Non-AKI	AKI
Onset of AKI, mean days ± SD	NA	6 ± 2.6
Change in Scr, fold increase from baseline (median, IQR)	1.3 (1.2, 1.5)*	1.9 (1.4, 2.5)*
Scr at discharge, mg/dl (median, IQR)	0.7 (0.5, 0.9)*	1.1 (0.7, 1.5)*
Patients with Scr above baseline at discharge	NA	19 (44)
Patients with 28-day mortality	9 (5)[Y]	7 (16)[Y]
LOS after VAN initiation (median, IQR)	9 (7, 14)*	13 (10, 23)*
LOS total (median, IQR)	11 (8, 17)*	15 (11, 23)*

[a] Where not otherwise noted, value is the no. (%) of patients. For non-AKI group, *n* = 184; for AKI group, *n* = 43. *, *P* value < 0.05, Wilcoxon-Mann-Whitney test; Y, *P* value < 0.05, chi-square test. NA, not applicable.

TABLE 4. Comparison of AKI patients using different definitions (AKIN vs NT)

Variable[a]	Value for group[b]	
	AKIN	NT[c]
Onset of AKI, mean days ± SD	5.9 ± 2.8	6.2 ± 2.4
No. of patients with:		
AKI staging		
AKIN		
Stage 1	24 (92)*	5 (29)*
Stage 2	2 (8)*	10 (59)*
Stage 3	0	2 (12)
RIFLE		
Risk	17 (68)*	3 (18)*
Injury	7 (28)*	11 (65)*
Failure	1 (4)	3 (18)
Change in Scr, fold increase from baseline (median, IQR)	1.6 (1.4, 1.9)[Y]	2.4 (2, 3)[Y]
Scr at discharge (median, IQR)	1.1 (0.7, 1.4)	1 (0.7, 2.3)
No. of patients with:		
Scr above baseline at discharge	11 (42)	8 (47)
Requirement of renal therapy/ intervention		
Renal consultation	3 (12)	6 (35)
Dialysis	0	0
Dosage adjustments for other meds	4 (15)	7 (41)
RPh renal monitoring	5 (19)	8 (47)
VAN discontinuation after AKI	6 (23)	8 (47)
Death	3 (12)	5 (29)
LOS after AKI, days (median, IQR)	7.5 (3, 13)	11 (5, 20)

[a] RPh, pharmacist; LOS, length of stay.
[b] For AKIN group, *n* = 26; for NT group, *n* = 17. Where not otherwise defined, parenthetical values are percentages. *, *P* value < 0.05, chi-square or Fisher's exact test; Y, *P* value < 0.05, Wilcoxon-Mann-Whitney test.
[c] NT patients met both AKIN and NT criteria.

29.5% overall. The incidence of AKI due to VAN reported in previous studies is variable, ranging from 11.6% to 42.6% (14). However, these studies defined AKI using the NT criteria. Our study found that AKI incidence according to NT criteria was 7.4%. The lower incidence of AKI in our study could be due to the fact that our patients were relatively healthy upon admission, with a median APACHE II score of 9 within 24 h of hospital admission in the AKI group.

In this study, using the AKIN definition for AKI, we identified baseline GFR, prior episode of AKI, concurrent ICU stay, and underlying malignancy to be significant predictors for developing AKI. Notably, in our study cohort, we did not find high VAN trough concentrations to be a predictor of AKI development. Although many patients in the study received concomitant nephrotoxic agents that could have contributed to their risk, we found through our multivariate analysis that it was not a significant predictor for developing AKI. A possible reason for this could be the awareness of VAN as a potential nephrotoxin, with prescribers and pharmacists thus being more diligent in limiting the duration of concurrent nephrotoxic therapies and closely monitoring renal function. In particular, concurrent vasopressors and other nephrotoxic agents were used for short durations (a median of 3 days). Twenty-eight percent of patients in the AKI group had vasopressor therapy, and many more patients (84%) received concomitant treatment with other nephrotoxic agents. Only 7% of AKI patients had concurrent use of an aminoglycoside. The inclusion of patients that received other nephrotoxic agents reflects practice in the real-world setting, since many patients with invasive infections often receive concomitant nephrotoxins.

Prior studies have found a significant association between VAN treatment duration and risk for developing AKI (10). In particular, Jeffres et al. found that a treatment duration of ≥14 days put patients at higher risk of developing AKI, defined as an Scr increase of ≥0.5 mg/dl (8). The incidence of AKI was greater when VAN therapy lasted ≥7 days in our study; however, the univariate analysis did not find the treatment duration to be a significant risk factor for developing AKI. However, only 5 of the AKI patients received VAN for ≥14 days, and thus the numbers may be too small for detecting any significance.

Previous studies have also shown that AKI can lead to poorer outcomes, including a longer length of hospital stay, increased mortality and morbidity, and increased cost of care (11). Our study had similar results since patients with AKI had a longer length of hospital stay and a higher risk of death. None of the AKI patients progressed to acute renal failure with the need for renal replacement therapy. Patients with AKI according to the NT criteria required more interventions, including renal consultations and dosage adjustments. Thus, the application of the AKIN criteria has the potential to identify at-risk patients earlier in the course of kidney injury, which may in turn require fewer interventions.

This study has several limitations. The study was performed at a single center limited to an elderly population. Since AKI was the primary focus of the study rather than efficacy, patients who received at least 5 days of VAN therapy were considered regardless of the indication for VAN as long as a VAN trough concentration was available. While our findings may be applicable broadly to relatively healthy elderly patients receiving VAN empirical therapy, our results may not be applicable to other settings, such as in patients with invasive infections and in the pediatric population. The study design was observational and did not investigate the outcome from a proactive interventional design. The VAN dosing protocol at our institution calls for the pharmacists to monitor clinical status and renal function closely and notify the physician if an episode of AKI occurs. However, our institution does not have a rigid documentation procedure of all interventions made that are accepted and denied. Thus, we were unable to monitor with certainty how many AKI cases were communicated to the physician and how many patients were changed to an alternative anti-infective agent as a result of pharmacist intervention. Finally, since a majority of the patients were on other nephrotoxic agents, the likelihood that an episode of AKI was directly related to VAN is difficult to conclude.

Conclusions. This study showed that AKIN criteria, compared to NT criteria, appear to be more sensitive and may offer the ability to identify AKI at earlier stages of injury. The AKIN criteria, which have been integrated into the VAN dosing protocol at our institution, may alert the physician and pharmacist to consider alternative therapies if there is a small but abrupt change in the patient's renal function. Significant risk factors for developing AKI included lower baseline GFR, a prior episode of AKI, a concurrent ICU stay, and malignancy. In this cohort of a relatively healthy elderly population receiving VAN empirical therapy, age, trough concentration of ≥15 μg/ml, and treatment duration were not risk factors for developing AKI associated with VAN therapy as defined by AKIN criteria. A prospective study controlled for timing and type of intervention upon diagnosis of AKI should be performed to validate the utility of new diagnostic criteria for AKI and the impact on patient outcomes.

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