Risk of acute kidney injury in critically ill surgical patients with presumed pneumonia is not impacted by choice of methicillin-resistant staphylococcus aureus therapy

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ABSTRACT

Background: Vancomycin and linezolid are standard treatment options for nosocomial methicillin-resistant Staphylococcus aureus (MRSA) pneumonia. While acute kidney injury (AKI) is commonly attributed to vancomycin, existing data has not definitely confirmed vancomycin as an independent risk factor for AKI.

Aims: This study aimed to quantify the incidence of AKI in Surgical Intensive Care Unit (ICU) patients receiving empiric vancomycin or linezolid for nosocomial pneumonia and to identify risk factors for AKI with a focus on MRSA antibiotic therapy.

Materials and Methods: A retrospective cohort analysis of surgical ICU patients who received at least 48 h of vancomycin or linezolid for pneumonia was performed. Patients who received vancomycin were compared to those who received linezolid with a primary endpoint of AKI as defined by the risk/injury/failure/loss/end-stage renal disease (RIFLE) criteria. A modified RIFLE criteria assessing only changes in serum creatinine was also used.

Results: One hundred one patients were evaluated (63 vancomycin and 38 linezolid). AKI occurred in 51 (81.0%) and 32 (84.2%) patients in the vancomycin and linezolid groups (P = 0.79), respectively. Using the modified RIFLE criteria, AKI occurred in 19 (30.2%) and 14 (36.8%) patients in the vancomycin and linezolid groups (P = 0.448). After adjustment for age, diabetes mellitus, Charlson comorbidity index, and concomitant nephrotoxins, there was no difference in risk of AKI between groups (P = 0.773).

Conclusions: Patients who received empiric vancomycin or linezolid for nosocomial pneumonia experienced high, but similar rates of AKI. The results suggest MRSA antibacterial therapy in this setting may not be independently indicative of AKI risk, rather the risk is likely multifactorial.

Key Words: Critical care, healthcare-associated infections, pneumonia, renal failure, vancomycin

INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) represents 10%–40% of nosocomial pneumonia infections. Antibiotics such as vancomycin or linezolid are recommended for empiric treatment of hospital-acquired pneumonia and ventilator-associated
pneumonia (VAP). While vancomycin is active against most Gram-positive bacteria, nephrotoxicity continues to be a concern with its use. The reported incidence of this side effect in Intensive Care Unit (ICU) patients ranges from 1% to 25% and carries a mortality rate of 15%–60%. In addition to potentially lower nephrotoxicity risk, superior tissue penetration, and 100% oral bioavailability are qualities that may make linezolid an attractive alternative to vancomycin for the treatment of MRSA pneumonia.

While vancomycin is commonly associated with nephrotoxicity, studies evaluating nephrotoxicity risk among MRSA-active agents such as vancomycin and linezolid are limited, and only one study has attempted to compare nephrotoxicity rates between these two antimicrobials in surgical ICU patients. The results from this study suggest linezolid is protective regarding rise in serum creatinine; however, nephrotoxin exposure was not accounted for in these patients. The aim of this study is to quantify the incidence of acute kidney injury (AKI) in surgical ICU patients receiving vancomycin or linezolid for empiric nosocomial pneumonia and to identify factors associated with AKI with a focus on MRSA antibiotic therapy. It is hypothesized that these patients treated with vancomycin will experience a similar rate of AKI compared to those treated with linezolid.

**MATERIALS AND METHODS**

**Study design and location**

This was a retrospective, risk factor analysis of surgical ICU patients treated empirically for pneumonia with linezolid or vancomycin at a 1321 bed, tertiary academic medical center. At this institution, the surgical ICU is a 38-bed mixed unit admitting burn, trauma, and surgical patients. The standard approach to diagnosis and management of pneumonia in the surgical ICU includes performing a nonbronchoscopic bronchoalveolar lavage (BAL) followed by empiric antibiotic initiation. As the performance of a BAL requires fellow or attending physician approval, this process is only performed if infection is suspected based on clinical parameters. In the surgical ICU, linezolid was the empiric antibiotic of choice for MRSA coverage for pneumonia until May 2015. After May 2015, vancomycin became the empiric antibiotic of choice in the surgical ICU due to a newly implemented linezolid restriction. Standard vancomycin dosing strategy includes a 25 mg/kg loading dose followed by 20 mg/kg maintenance dosing with a maximum of 2 g per dose and frequency based on renal function. At this medical center, it is common practice to discontinue empiric MRSA therapy once no Gram-positive cocci are reported on Gram stain. No other practice changes related to the diagnosis and management of pneumonia occurred in the surgical ICU during the period included in this study. This study was granted exemption by the Institution Review Board.

**Patient population**

To meet inclusion criteria, patients needed to be admitted to the surgical ICU between October 1, 2014 and September 30, 2015 and have received empiric antibiotic treatment for nosocomial pneumonia with either linezolid or vancomycin for at least 48 h. Empiric antibiotic coverage of pneumonia was defined as the occurrence of a BAL within 24 h of vancomycin or linezolid initiation. Patients who were pregnant, incarcerated, and >89 or <18 years of age were excluded from this study. All patients who had a previous diagnosis of end-stage renal disease (chronic kidney disease [CKD] Stage V), received any renal replacement therapy (RRT) before antibiotic initiation, or received both vancomycin and linezolid were also excluded from this study.

**Outcome measures and data collection**

The primary outcome was the development of new AKI defined by the risk/injury/failure/loss/end-stage renal disease (RIFLE) criteria. A modified RIFLE criteria [Table 1] utilizing only the changes in serum creatinine was also evaluated due to limitations with urine collection and documentation within the electronic medical record and is a method commonly used to classify acute renal dysfunction and nephrotoxicity. Patients were evaluated for the development of AKI and for risk factors for AKI during the period between 48 h before initiation and 48 h after discontinuation of MRSA antibiotic therapy (vancomycin or linezolid). Secondary endpoints included initiation of new RRT during antibiotic treatment, ICU and hospital length of stay, and all-cause hospital mortality.

Patient demographics and clinical characteristics were collected from the patients’ electronic medical records. Age, gender, body mass index, comorbidities,
and the Charlson comorbidity index were collected to describe the patient population. The following variables were collected 48 h before antibiotic initiation: the acute physiology and chronic health evaluation (APACHE) II score, serum creatinine, and ventilator status. Urine output and minimum and maximum serum creatinine were reviewed to determine the development of AKI. Duration of antibiotic therapy and vancomycin troughs (defined as a steady state serum level collected <2 h before the next dose) were collected. Potential risk factors for AKI such as use of vancomycin or linezolid, hypotensive episodes defined as mean arterial pressure <65 mmHg, any occurrence of nephrotoxin exposure, and number of surgical operations were also collected. The following were considered nephrotoxic medications: intravenous contrast dye, aminoglycosides, nonsteroidal anti-inflammatory drugs, amphotericin B, vasopressors, immunosuppressants such as cyclosporine and tacrolimus, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, diuretics, intravenous acyclovir, trimethoprim/sulfamethoxazole, piperacillin/tazobactam, and others (i.e., polymyxin B).

Statistical analysis
Patient demographics and clinical characteristics were compared between patients receiving vancomycin and linezolid. Patient characteristics are presented as frequencies and percentages for categorical variables while continuous variables are presented as mean ± standard deviation or median (25%–75% interquartile range) as appropriate. Pearson Chi-square was used to compare differences in categorical variables, whereas the two-sample Student’s t-test or Wilcoxon rank-sum test were used for continuous variables as appropriate.

To identify factors associated with AKI while focusing on MRSA antibiotic therapy, patients who developed AKI were compared to patients who did not develop AKI based on the modified RIFLE criteria. Logistic regression was used to find the association between the onset of AKI and MRSA therapy (vancomycin vs. linezolid). Both the unadjusted and the adjusted odds of AKI for vancomycin compared to linezolid (referent group) are presented. The adjusted odds ratios (OR) are based on a risk factor modeling approach where the goal is not to predict AKI but to find the true relationship between AKI and MRSA therapy. Thus, a covariate is only entered into the model if it is a confounder or an effect modifier of the relationship between AKI and MRSA therapy. A confounder is defined if the AKI odds ratio for vancomycin changes by 10% in either direction when the covariate is entered into the model compared to when it was not in the model. An effect modifier is defined when the covariate has a statistically significant interaction with the risk factor (interaction \(P \leq 0.05\)). All analyses were run using Stata 14.0, StataCorp, College Station, TX, USA.

RESULTS

Patient characteristics
Five hundred and eighty-nine patients were screened for eligibility, with 101 meeting all inclusion/exclusion criteria (63 received vancomycin and 38 received linezolid). Of those included 27 received vancomycin before May 2015 linezolid restriction in the surgical ICU and 4 received linezolid after this change. The primary reasons for exclusion were the lack of a BAL \((n = 312)\), collection of a BAL without initiation of antibiotics within 24 h \((n = 74)\), <48 h of MRSA therapy \((n = 49)\), and use of both vancomycin and linezolid \((n = 24)\).

Baseline characteristics were similar for patients receiving vancomycin or linezolid, although a higher proportion of patients in the linezolid group had a history of diabetes mellitus or CKD Stages I–IV [Table 2]. The median duration of antibiotic therapy was 3.0 (3.0–5.0) days for vancomycin and 5.0 (3.0–8.0) days for linezolid-treated patients. Troughs were obtained in 41 (65.1%) patients receiving vancomycin with a median concentration of 14.3 (9.5–21.4) mg/L. Thirteen (31.7%) of those patients had a trough above 20.0 mg/L, of which twelve (92.3%) were exposed to two or more nephrotoxins and seven (53.8%) went on to develop AKI. Three (4.8%) received a total daily dose of vancomycin over 4 g.

The majority of patients were exposed to two or more nephrotoxins with 52 (82.5%) patients in the vancomycin group and 45 (60.5%) patients in the linezolid group.

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| Table 2: Characteristics for vancomycin- and linezolid-treated patients |
|-----------------------------|-----------------------------|
| **Vancomycin (n = 63)**    | **Linezolid (n = 38)**     |
| **Baseline characteristics** |                             |
| Age (years) *               | 57.3 (16.3)                 |
| Male gender i               | 39 (61.9)                   |
| BMI (kg/m²) *               | 28.8 (7.3)                  |
| APACHE II *                 | 22 (17-25)                  |
| Ventilator-associated pneumonia ii | 32 (50.8)                 |
| Charlson comorbidity index i | 2 (1.0-6.0)                 |
| Hypertension                | 34 (53.9)                   |
| Diabetes mellitus           | 10 (15.9)                   |
| Chronic kidney disease      | 4 (6.3)                     |
| Congestive heart failure    | 4 (6.3)                     |
| Peripheral vascular disease | 3 (4.8)                     |
| Renal transplantation       | 0                           |
| Number of surgical operations |                             |
| 0                           | 41 (65.0)                   |
| 1                           | 19 (30.2)                   |
| 3                           | 3 (4.8)                     |

*Mean (SD). iMedian (interquartile range). †n (%). ‡Time between 48 h before initiation and after discontinuation of MRSA antibiotic therapy. APACHE: Acute physiology and chronic health evaluation, BMI: Body mass index, SD: Standard deviation, MRSA: Methicillin-resistant Staphylococcus aureus.
group and 34 (89.5%) in the linezolid group. Figure 1 further describes the relationship between total number of nephrotoxic agents and development of AKI based on MRSA antibiotic. The most commonly prescribed concomitant nephrotoxic agents in the entire cohort were piperacillin/tazobactam (n = 77), IV contrast dye (n = 55), diuretics (n = 42), vasopressors (n = 34), and aminoglycosides (n = 30). The distribution of these nephrotoxins was similar between the vancomycin and linezolid groups.

Clinical outcomes
AKI defined by RIFLE criteria was identified in 51 (81.0%) patients in the vancomycin group and 32 (84.2%) patients in the linezolid group (P = 0.7917). Using the modified RIFLE criteria, 19 (30.2%) vancomycin patients and 14 (36.8%) linezolid patients developed AKI (OR = 0.74; 95% confidence intervals [CI]: 0.32–1.73; P = 0.448) [Figure 2]. The median day to maximum serum creatinine was 4 (2–6) for vancomycin and 4 (3–6) for linezolid patients. Age, diabetes mellitus, Charlson comorbidity index, and number of nephrotoxin exposures were variables that confounded the relationship between MRSA therapy (vancomycin vs. linezolid) and AKI by at least 10% and were included in the multivariable analysis. After adjustment for these variables, the 12% reduction in the odds of AKI for vancomycin compared to linezolid was not statistically significant (OR = 0.88, 95% CI: 0.36–2.15; P = 0.773) [Table 3].

All-cause mortality was observed in 15 (23.8%) and 11 (29.0%) patients receiving vancomycin and linezolid, respectively. Four patients from the entire cohort were initiated on RRT during antibiotic therapy, 1 (1.6%) in the vancomycin group and 3 (7.9%) in the linezolid group. The median hospital length of stay was 22.0 (14.0–35.0) days in the vancomycin group and 25.5 (16.0–43.0) days in the linezolid group. The median ICU length of stay was found to be 17.0 (9.0–27.0) days in patients receiving vancomycin and 21.5 (10.0–34.0) days in patients receiving linezolid.

DISCUSSION
This study failed to find a statistically significant difference in the incidence of AKI between patients who received vancomycin or linezolid for the empiric treatment of nosocomial pneumonia. Risk factors such as age, diabetes mellitus, Charlson comorbidity index, and nephrotoxin exposure were found to impact the relationship between MRSA therapy and AKI; however, neither these factors nor the choice of linezolid versus vancomycin was determined to independently impact the risk of AKI. To the best of our knowledge, this risk factor analysis is the first to retrospectively evaluate the incidence of AKI between vancomycin and linezolid while also accounting for other potential risk factors of AKI.

Although several recent studies have aimed to identify the comparative risk of AKI between vancomycin- and

Table 3: Multivariable analysis evaluating adjusted odds ratio of acute kidney injury

| Variable                  | OR (95% CI)     | P    |
|--------------------------|-----------------|------|
| 1 year increase (age)    | 0.99 (0.97-1.02)| 0.54 |
| Diabetes mellitus        | 1.41 (0.50-4.01)| 0.52 |
| Charlson comorbidity index | 1.04 (0.93-1.17)| 0.47 |
| Number of nephrotoxins   | 1.14 (0.80-1.62)| 0.48 |
| Vancomycin               | 0.88 (0.36-2.15)| 0.77 |

OR: Odds ratio, CI: Confidence interval

Figure 1: (a) Total number of concomitant nephrotoxins received for vancomycin-treated patients (b) Total number of concomitant nephrotoxins received for linezolid-treated patients

Figure 2: Incidence of acute kidney injury as defined by the modified RIFLE criteria for vancomycin- and linezolid-treated patients
linezolid-treated patients, to date, the results are inconclusive and conflicting.\cite{3,8,10-12,14,15} Peyrani et al. evaluated nephrotoxicity as a secondary outcome in ICU patients. Nephrotoxicity in those receiving MRSA VAP therapy in the ICU occurred in 14.9% of vancomycin and 10.9% of linezolid patients. Similar to the current study, this difference also lacked statistical significance.\cite{10} A retrospective, cohort study of 227 patients treated for MRSA hospital-acquired pneumonia with vancomycin or linezolid also found no difference in rates of nephrotoxicity.\cite{11} In contrast, Wang et al. performed a meta-analysis of nine randomized controlled trials that found a trend toward higher nephrotoxicity with vancomycin use compared to linezolid in suspected MRSA nosocomial pneumonia.\cite{14} This meta-analysis evaluated studies in which nephrotoxicity was a secondary outcome that also made no adjustments for potential contributing factors. Davies et al. attempted to retrospectively quantify the increased risk of nephrotoxicity with vancomycin use in ICU patients as a primary patient outcome. While linezolid was determined to be protective with regards to rise in serum creatinine; this outcome may lack external validity and should be interpreted with caution as patients were excluded if any nephrotoxic antibiotics were administered. In addition, the use of other concomitant nonantimicrobial nephrotoxins such as vasopressors and intravenous contrast dye was not reported or accounted for.\cite{8} A common limitation in both Wang et al. and Davies et al., which was accounted for in the current study, was the use of concomitant nephrotoxins. Due to this, our results further challenge the concept behind vancomycin-induced nephrotoxicity and support the idea that AKI is a multifactorial complication seen in critically ill patients.

Regardless of the definitions used to identify AKI (i.e., RIFLE criteria or modified RIFLE criteria limited to changes in serum creatinine), the incidence of AKI observed in the current study was substantially higher than previously reported. Several studies suggest the incidence of nephrotoxicity among non-ICU patients receiving vancomycin or linezolid for MRSA pneumonia is <5%.\cite{3,15} As the level of patient acuity increases, a higher rate of AKI is commonly observed. In two studies of ICU patients with a large proportion of VAP, the incidence of AKI, defined as an increase in serum creatinine of 0.5 mg/dL or 50% above baseline, occurred in 14.9%–18.2% and 8.4%–10.9% of those receiving vancomycin or linezolid, respectively.\cite{11,10} Using the RIFLE criteria, Davies et al. determined the rate of AKI in ICU patients with MRSA pneumonia to be 22.1% when treated with vancomycin and 16.6% when treated with linezolid.\cite{8} The definitions for AKI in these studies all have the risk of overestimating the incidence of nephrotoxicity compared to the modified RIFLE criteria used in the current study [Table 1]. For example, an increase in serum creatinine from 2.0 to 2.5 mg/dL would only be considered AKI using the increase of 0.5 mg/dL or 50% above baseline approach. In addition, as seen in the current study, incomplete urine output documentation could only lead to AKI using the RIFLE criteria.

Despite using the modified RIFLE criteria, the population in our study experienced AKI in 30.2% of vancomycin-treated patients and 36.8% of linezolid-treated patients. As suggested in the previously published literature, the high incidence of AKI in our study is likely multifactorial and unique to the patient population included in this study.\cite{16-18} In the current study, patients were admitted to the surgical ICU, had a high severity of illness as indicated by elevated APACHE II scores, and presented with several comorbidities on admission that would place this population at an inherently higher risk of developing AKI. All-cause mortality ranged from 23.8% to 29.0% with a median ICU length of stay between 17 and 21.5 days further describing our patients’ severity of illness. Furthermore, neither supratherapeutic vancomycin troughs nor prolonged treatment duration was a factor as the median trough was 14.3 mg/L and median duration of MRSA-directed antibiotic therapy was 3.0 (3.0–5.0) and 5.5 (3.0–8.0) days for vancomycin and linezolid, respectively. In addition, these patients were exposed to multiple concomitant AKI risk factors such as nephrotoxic medications, intravenous contrast dye, periods of hypotension, and surgical operations. These variables were not collected, not accounted for, in previously published literature. The combination of these inherent and external risk factors places this population at a higher risk for developing AKI, irrespective of MRSA therapy.

Several limitations of the present study should be noted. It was estimated that 97 patients per group would have at least 80% power to detect a difference in AKI between groups based on published rates of AKI in patients receiving linezolid or vancomycin. The present study did not reach this sample size and is therefore underpowered. Selection bias favoring linezolid use among patients at higher risk for AKI may have been introduced when antibiotic selection occurred. However, of the four patients who received linezolid after May 2015, two had true clinical indications for linezolid (i.e., vancomycin allergy, history of vancomycin-resistant Enterococcus), whereas the other two had documentation of selection bias toward linezolid due to concerns for renal toxicity. Neither patient with selection bias was found to develop AKI during antibiotic therapy. Patients receiving linezolid had a higher Charlson comorbidity index, higher incidence of diabetes mellitus, and CKD Stages I–IV on admission, an elevated baseline serum creatinine, a higher incidence of hypotension, and increased concomitant nephrotoxin exposure suggesting these patients were already at a higher risk of developing AKI. Despite adjusting for several of these factors
using multivariable analysis, a small sample prevented inclusion of all possible risk factors that may have contributed to the observed decreased incidence of AKI in vancomycin patients. Although patients requiring RRT before antibiotic initiation were excluded from the analysis, we were unable to identify patients with AKI before treatment potentially confounding outcomes.

CONCLUSIONS

Patients who received vancomycin or linezolid for the empiric treatment of nosocomial pneumonia experienced high, but similar rates of AKI. This finding supports the authors’ hypothesis that surgical ICU patients are at a similar risk of AKI when empirically treated with vancomycin or linezolid. Multivariable analysis accounting for age, diabetes mellitus, Charlson Comorbidity Index, and nephrotoxin exposure found vancomycin was associated with a reduction in risk of AKI compared to linezolid, although this was not statistically significant. The results presented in this risk factor analysis suggest MRSA therapy for empiric treatment of nosocomial pneumonia in surgical ICU patients may not be independently indicative of AKI risk, rather this is likely a multifactorial outcome. Future studies of larger cohorts are warranted to further describe comparative AKI risk between vancomycin and linezolid.

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Conflicts of interest
There are no conflicts of interest.

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