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Vancomycin Area Under the Curve and Acute Kidney Injury: A Meta-analysis

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Background. This study analyzed the relationship between vancomycin area under the concentration-time curve (AUC) and acute kidney injury (AKI) reported across recent studies.

Methods. A systematic review of PubMed, Medline, Scopus, and compiled references was conducted. We included randomized cohort and case-control studies that reported vancomycin AUCs and risk of AKI (from 1990 to 2018). The primary outcome was AKI, defined as an increase in serum creatinine of ≥0.5 mg/L or a 50% increase from baseline on ≥2 consecutive measurements. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Primary analyses compared the impact of AUC cutpoint (greater than ~650 mg × hour/L) and AKI. Additional analysis compared AUC vs trough-guided monitoring on AKI incidence.

Results. Eight observational studies met inclusion/exclusion criteria with data for 2491 patients. Five studies reported first-24-hour AUCs (AUC0-24) and AKI, 2 studies reported 24- to 48-hour AUCs (AUC24-48) and AKI, and 2 studies reported AKI associated with AUC- vs trough-guided monitoring. AUC less than approximately 650 mg × hour/L was associated with decreased AKI for AUC0-24 (OR, 0.36 [95% CI, .23–.56]) as well as AUC24-48 (OR, 0.45 [95% CI, .27–.75]). AKI associated with the AUC monitoring strategy was significantly lower than trough-guided monitoring (OR, 0.68 [95% CI, .46–.99]).

Conclusions. AUCs measured in the first or second 24 hours and lower than approximately 650 mg × hour/L may result in a decreased risk of AKI. Vancomycin AUC monitoring strategy may result in less vancomycin-associated AKI. Additional investigations are warranted.

Keywords. vancomycin; AUC; nephrotoxicity.

Vancomycin is a drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) in a variety of infections [1–3]. The consensus vancomycin guidelines published in 2009 by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists proposed an efficacy target for vancomycin area under the concentration-time curve (AUC)/minimum inhibitory concentration (MIC) ratio of >400 mg × hour/L (ie, the AUC relative to the MIC) for MRSA isolates with MIC of ≤1 mg/L [4]. It also recommended maintaining a trough concentration between 15 and 20 mg/L to facilitate achieving the target AUC/MIC of ≥400. This trough target has resulted in debate about whether the goal could be safely reached [5–7]. Trough concentrations have been demonstrated to misclassify true AUC because of significant interpatient variability [6]; thus, at a minimum, the target has been suggested as imprecise. Additionally, vancomycin is a known nephrotoxin. In a prospective study, vancomycin administration resulted in an absolute increase of 10% in acute kidney injury (AKI) (from 8.4% to 18.2%) [8].

Multiple studies have evaluated the association between trough levels and vancomycin-associated acute kidney injury (VIKI) and an exposure–response relationship has been demonstrated [9–14]. Lodise and colleagues [11] found a risk of VIKI of 5% with initial troughs of <10 mg/L compared to VIKI rates of 21% with troughs of 10–15 mg/L, 20% with 15–20 mg/L, and 33% with >20 mg/L. Other studies have reported relatively similar risks of VIKI with different troughs [10, 15, 16]. Therefore, targeting a trough concentration of 15–20 mg/L may result in unnecessary drug exposure and hence increase the risk of AKI. While several investigations have explored the impact of higher average vancomycin exposure (eg, AUC) on the risk of AKI, the AUC threshold for AKI has not been clarified [11, 17, 18]. Therefore, we conducted a meta-analysis to quantify the relationship between vancomycin AUC and AKI reported across all published studies.

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METHODS

Search Strategy

A comprehensive literature search was conducted embracing Cochrane handbook methodology [19] from 1 January 1990 to 31 January 2018. We limited our search to PubMed, Embase, and Scopus. We also manually reviewed the references listed in articles met inclusion criteria to identify additional relevant literature. Search terms included "vancomycin," "nephrotoxicity," "renal injury," "AUC," "area under the curve," "trough," "continuous," and "intermittent." Medical Subject Heading terms and Emtree entries in addition to the appropriate Boolean operators (ie, OR, AND, NOT) were combined to make a search strategy. Results were limited to articles and posters available in English.

Inclusion Criteria

A study was eligible if it met the following criteria: (1) adult human participants who received intravenous vancomycin; (2) AKI was measured as an outcome; and (3) AUC was calculated and compared between those with AKI and those that did not experience AKI. Case reports were excluded but references from case reports were reviewed. In reviewing the articles, the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines were followed [20]. The screening initially started with screening titles and abstracts. Studies were excluded based on abstract if they did not report AKI as a safety outcome or if they were conducted on animals.

Data Extraction

Data extraction was performed using a data extraction table (see Supplementary Appendix). The following was obtained for each study: studies characteristics (authors, publication year, study design, country, and clinical trials registration number), patient population (sample, demographics, renal functions, and severity of illness), vancomycin (dosage, frequency, duration of therapy, AUCs, and troughs), infection-related information (site of infection and bacteria isolated species), and nephrotoxicity outcomes.

Outcomes

The main outcome for this meta-analysis was incidence of AKI, which was defined as an increase in serum creatinine of ≥0.5 mg/L or a 50% increase from baseline on ≥2 consecutive measurements [4, 21]. Primary analyses compared the impact of AUC (>650 or <650 mg × 24 hour/L) and AKI. For category binning, the cutpoint utilized by the primary authors was accepted if it was ±100 mg × 24 hour/L. AUCs were stratified by those that were calculated over the first and second 24-hour periods ($AUC_{0\text{-}24}$ and $AUC_{24\text{-}48}$, respectively). Because the identified studies reported AUC values between 550 and 700 mg × hour/L and the lone prospective study identified a cutpoint of 650 mg × hour/L, a dichotomous endpoint of 650 mg × hour/L was utilized to unify low vs high AUC (and denoted ~650 mg × hour/L.) Reported number of AKI cases secondary to high vs low AUC were used as reported in original articles using their AUC thresholds of toxicity. An additional analysis compared AUC- vs trough-based therapeutic drug monitoring on AKI incidence.

Quality Assessment

Quality of the included studies was assessed by 2 independent investigators. Because all included studies were observational, the Newcastle-Ottawa scale was used to assess their quality [22]. After independent review, any differences were discussed between the investigators. Any disagreement was settled by a third investigator (M. H. S.).

Statistical Analysis

Analyses were performed using Cochrane systematic review software Review Manager (RevMan version 5.3.5; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, 2014). Heterogeneity (I^2) was assessed using χ^2 test ($P < .1$ and I^2 of >50% were used to indicate significant heterogeneity). The preplanned analysis conformed to the following: odd ratios (ORs) with 95% confidence intervals (CIs) were estimated using fixed-effects models when heterogeneity was not significant, and random-effects models were employed if heterogeneity was significant.

RESULTS

Study Description

An initial search identified 376 studies (Supplementary Figure 1). A total of 208 studies were selected after removal of duplicates. Of the 208 studies, 168 studies were not eligible to be included in our analysis during the title and abstract screening. Full-text review was required for a total of 40 studies. Out of these 40 studies, only 8 studies met our inclusion criteria [23–30]. Reasons for study exclusion were as follows: (1) not relevant (ie, conducted in pediatric population or animal studies); (2) did not report AUC; or (3) safety was not reported. No additional studies met inclusion criteria after reviewing references of the evaluated articles. No randomized controlled trials were identified. All 8 studies were observational cohort investigations, of which 6 were retrospective and 2 were prospective. Of those included studies, 5 reported vancomycin exposures in $AUC_{0\text{-}24}$, 2 reported $AUC_{24\text{-}48}$ exposures, and 2 assessed using AUC vs trough monitoring strategy and incidence of nephrotoxicity. A summary of the studies included is shown in Table 1.

A total of 2491 patients participated in the 8 included studies, of which 911 patients received an AUC-monitoring strategy for vancomycin [29, 30]. The rest of the patients were treated under a trough-guided approach. Details on dosing regimens used in each of the included studies and patients' baseline characteristics can be found in Table 2. AUC nephrotoxicity

Table 1. Details of the Included Studies

Study	Study Design	Country	Total Population, No.	Study Objective	AUC Estimation Method	Relevant Findings
Allen 2017 [25]	Single-center retrospective cohort study	US	278	Evaluate relationship between vancomycin $AUC_{0\text{-}24}$ and nephrotoxicity	Bayesian approach	Significant increase in nephrotoxicity at AUC ≥ 700 mg × h/L
Chavada 2017 [24]	Single-center retrospective observational cohort study	Australia	127	Evaluate PK criterion predicting AKI for vancomycin TDM	Bayesian approach	Higher vancomycin troughs associated with AKI
Jumah 2018 [26]	Single-center retrospective cohort study	US and Singapore	57	PK/PD determinants of vancomycin efficacy	Bayesian approach	Vancomycin AUC/MIC_{Etest} value of ≥389 achieved within 72 h as associated with reduced mortality
Suzuki 2012 [27]	Retrospective study	Japan	37	Evaluate need of C_{max} for vancomycin TDM	Bayesian approach	C_{min} and $AUC_{0\text{-}24h}$ are equally useful in predicting safety of vancomycin
Zasowski 2017 [23]	Multicenter retrospective cohort study	US	323	Examine association of initial vancomycin AUC and AKI	Bayesian approach	Vancomycin AUC_{24} therapeutic ceiling is 700 mg × h/L
Neely 2018 [30]	Prospective cohort study	US	252	Cost-benefit analysis of trough vs AUC dosing	Bayesian approach	AUC TDM: fewer blood samples, shorter duration of therapy, reduced AKI rates
Finch 2017 [29]	Single-center, retrospective, quasi-experimental study	US	1280	Assess impact of switch to AUC dosing	2-level estimation approach	AUC dosing was associated with less frequent nephrotoxicity
Lodise 2017 [28]	Prospective multi-center observational study	US	256	Assess a prospective multicenter approach to AUC-dosing investigation	Bayesian approach	Achieving higher VAN $AUC_{day\ 2}$/MIC exposures in patients with MRSA bacteremia resulted in increased AKI

Abbreviations: AKI, acute kidney injury; AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve in the first 24 hours; C_{max}, maximum concentration; C_{min}, minimum concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PK/PD, pharmacokinetic/pharmacodynamic; TDM, therapeutic drug monitoring; US, United States; VAN, vancomycin.

thresholds reported in 5 of the included studies ranged between 550 and 700 mg × hour/L. Chavada and colleagues [24] found an association between an $AUC_{0\text{-}24}$ of 563 mg × hour/L (using classification and regression tree [CART] analysis) and AKI in patients receiving vancomycin for MRSA bacteremia. Using the same analysis strategy, Zasowski et al [23] detected an $AUC_{0\text{-}24}$ of 677 mg × hour/L and $AUC_{24\text{-}48}$ of 683 mg × hour/L as threshold of AKI for patients on vancomycin for MRSA bacteremia and pneumonia. Similarly, Allen and colleagues [25] observed an association between higher

Table 2. Patient Population Information

	Patient Demographics			Vancomycin (TDM)				Infection Information
Study	Age, y	Renal Function CrCl, mL/min	APACHE-II, Mean	Dose	Duration, d	AUC, mg × h/L	Trough, mg/L	Bacterial Species
Allen 2017 [25]	NR	Normal	NR	≥4 g/d	≥72	≥700 vs <700	>20	NR
Chavada 2017 [24]	≥18	Not specified	NR	NR	14	>563	17.2	MRSA BSI
Jumah 2018 [26]	75	Not specified	12	1 g/d	14	<389 vs ≥389	15–20	*Enterococcus*
Suzuki 2012 [27]	73 ± 9.2	61.8 ± 31.4	NR	NR	12	629.1 ± 272.8	16.3 ± 6.8	MRSA
Zasowski 2017 [23]	Mean: 61.7	Varied	13	NR	6	0–24 h: 572; 0–48 h: 586	0–24 h: 11.1; 0–48 h: 13.6	NR
Neely 2018 [30]	Year 1: 47.7; Year 2: 48	Not specified	NR	NR	Year 1: 8.2; Year 2: 5.4	Year 1: 510; Year 2: 459	Year 1: 14.4; Year 2: 9.7	MSSA, MRSA, CoNS, Viridans streptococci
Finch 2017 [29] (AUC vs Trough based dosing)	59.1 ± 16.9	Trough: 80.1; AUC: 78.3	Trough: 12; AUC: 14	NR	Trough: 5.6; AUC: 5.3	Trough: NR; AUC: 471.5	Trough: 15; AUC: 12	NR
Lodise 2017 [28]	Mean: 61	NR	12	NR	18	0–48 h: 586.9	NR	MRSA BSI

Abbreviations: APACHE-II, Acute Physiologic Assessment and Chronic Health Evaluation; AUC, area under the concentration-time curve; BSI, bloodstream infection; CoNS, coagulase-negative *Staphylococcus aureus*; CrCl, creatinine clearance; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NR, not reported; TDM, therapeutic drug monitoring.

incidence of AKI and AUC_{0-24} of ≥700 mg × hour/L. Suzuki et al [27], on the other hand, evaluated vancomycin exposure in patients with MRSA pneumonia. Nephrotoxicity incidence in patients with AUC >600 mg × 24 hour/L was significant. Yet Jumah and colleagues' [26] primary goal was to look into efficacy outcomes and vancomycin exposure in patients with enterococcal bacteremia; AKI incidence was also assessed. An average of AUC of approximately 650 mg × hour/L was reported in patients with AKI.

Quality of the Included Studies

Quality assessment of the included articles is shown in (Supplementary Table 3). The independent reviewers agreed universally on study classification. Six studies completely accounted for the 8 factors according to the Newcastle-Ottawa scale. One study was adequate in 7 factors, and one other study was adequate in 6 factors. In general, studies included did not show major problems of selection bias or performance bias.

Outcomes

AUC Thresholds

Five studies investigated the association between AUC_{0-24} and VIKI [23–28]. Significant heterogeneity was not detected among the included studies (P = .21; I^2 = 31%; Figure 1). Compared with high AUC_{0-24} (approximately >650 mg × hour/L), lower AUC_{0-24} had significantly lower risk of AKI (OR, 0.36 [95% CI, .23–.56]). When assessing the temporality of AUC calculation, 2 other studies examined the 48-hour period (AUC_{24-48}) [23, 28]. Lower AUC_{24-48} approximately <650 mg × hour/L was significantly associated with reduced incidence of VIKI (OR, 0.45 [95% CI, .27–.75]) (Figure 1).

AUC-guided Versus Trough-guided

Two studies utilized AUC-monitoring strategies for therapeutic adjustment (as opposed to trough-monitoring strategies) [29, 30]. No significant heterogeneity among these 2 studies was detected (P = .24, I^2= 26%; Figure 2). Acute kidney injury associated with vancomycin AUC monitoring strategy was significantly lower than with the trough-monitoring approach (OR, 0.68 [95% CI, .46–.99]).

DISCUSSION

This meta-analysis identified a clear exposure–response relationship within the published studies between vancomycin AUC and AKI. Furthermore, compilation of the emerging data on AUC-based monitoring strategies demonstrate that AKI can potentially be decreased by using an AUC monitoring strategy as opposed to status quo trough-based monitoring strategies. As vancomycin remains the second most administered antibiotic in the hospital setting, safety is paramount [31].

To the best of our knowledge, this is the first meta-analysis to explore the association between multiple reported vancomycin AUC exposures and incidence of nephrotoxicity. Eight studies of good quality were systematically evaluated. Our findings suggest that AUC of approximately ≤650 mg × 24 hour/L is associated with lower incidence of AKI. Furthermore, in a subgroup analysis, we found that using a vancomycin AUC monitoring strategy may reduce vancomycin-induced nephrotoxicity.

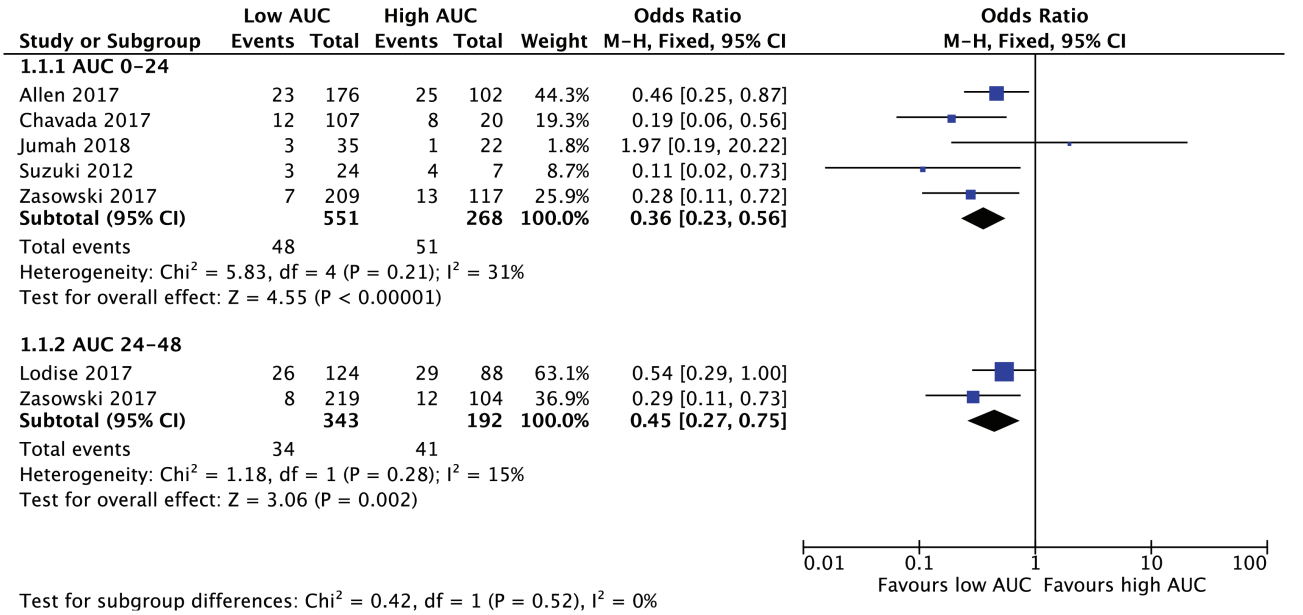

Figure 1. Forest plot indicating the association between vancomycin area under the curve compiled in the first 24 hours and nephrotoxicity. Abbreviations: AUC_{0-24}, area under the concentration-time curve compiled in the first 24 hours; AUC_{24-48}, area under the concentration-time curve compiled in the second 24 hours; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

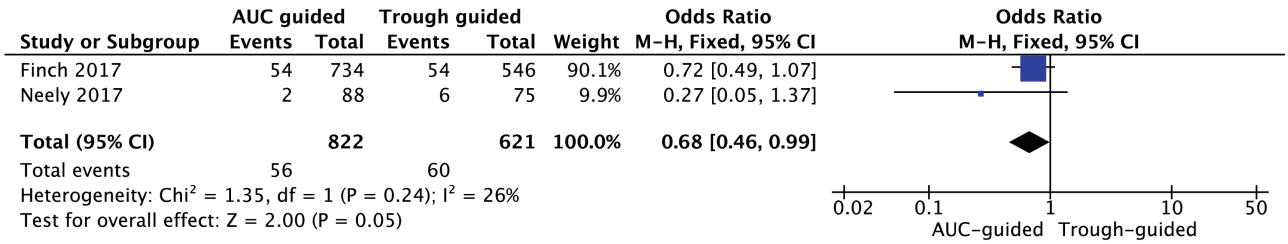

Figure 2. Forest plot indicating the risk of nephrotoxicity associated with AUC-guided vs trough-guided monitoring of vancomycin. Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

The association between vancomycin trough concentrations and AKI has been more extensively explored than exposure measured as AUC [9–11]. Van Hal and colleagues [9], conducted one of the largest meta-analyses in which 15 studies were included to assess the correlation between troughs >15 mg/L and vancomycin-induced nephrotoxicity. Troughs >15 mg/L were found to have greater risk of nephrotoxicity. Reported incidence of nephrotoxicity though was common among critically ill patients and patients who received concomitant nephrotoxins. These findings are aligned with multiple other studies that found multiple risk factors can potentiate vancomycin-induced nephrotoxicity such as higher troughs (>20 mg/L) or doses (>4 g/day), concurrent administration of nephrotoxins, and patient populations including obese persons, critically ill persons, and those with deep visceral infections [8, 32–34]. In our review, one study [24] reported concomitant nephrotoxins as an independent risk factor for VIKI, whereas another study [25] could not find an impact of concomitant nephrotoxins on VIKI, which can be explained by the small number of patients included in the second study. Severity of illness was evaluated in only 2 of the included studies [23, 30]; in one study, Zaswoski and colleagues [23] found that patients who experienced nephrotoxicity had higher APACHE-II scores compared with patients who did not experience VIKI (20.5 vs 13; $P = .001$).

Vancomycin kidney injury is mediated by either peak concentration (ie, C_{max}) or overall exposure (ie, AUC), whereas trough concentrations are less responsible for toxicity [12, 14]. This may have future implications for future dosing of vancomycin; however, it is not known if the AUC thresholds from different dosing profiles (eg, intermittent infusion vs continuous infusion) will be similar. In our subanalysis of the 2 studies that employed AUC monitoring strategy and compared it to the trough monitoring approach [29, 30], the risk of nephrotoxicity secondary to vancomycin was significantly lower with AUC-guided monitoring methods. Several observational and randomized controlled trials proposed administering vancomycin as a continuous infusion to reduce the risk of VIKI [35, 36]. Hanrahan and colleagues [36] conducted an observational study among 1430 critically ill patients. After multivariate adjustment, they found that continuous infusion was significantly less likely to cause nephrotoxicity. In another meta-analysis that included Hanrahan et al (2014), the authors found a trend for reduced risk of nephrotoxicity with continuous infusion (risk ratio, 0.8; $P = .3$); however, there was no mortality benefit observed with continuous infusion [37]. Like with the continuous infusion studies, we were not able to identify any mortality benefit in our meta-analysis due to a lack of published studies that reported efficacy endpoints along with safety of AUC monitoring strategy. While the optimal method of vancomycin monitoring remains uncertain, AUC monitoring strategy provides a promising safety profile when compared to the current standard of care (ie, trough-guided). There is not yet consensus on the optimal method to estimate AUC and heterogeneity exists in practice. Bayesian methods are generally more precise when the population used to build the model is appropriate for the population of intended application [30]; however, many clinical sites do not have access to Bayesian software or the expertise needed to build models for local use. Most studies included in this meta-analysis utilized a Bayesian approach with the exception that Finch and colleagues [29] used 2-level AUC estimation (Table 1). The difference in AUC estimation methods creates some heterogeneity and makes defining a precise threshold for renal toxicity difficult (especially in the setting that clinical strategies will differ in practice and patient populations will be varied). Thus, we caution against setting a hard fence at an AUC of 650 mg × hour/L since toxicity occurs via a continuum. It is important to note that trough-monitoring strategy was associated with higher incidence of nephrotoxicity. Moreover, regardless of the AUC estimation methods used, AUC monitoring strategies (when compared to trough monitoring strategies) utilized lower doses of vancomycin and resulted in less adverse renal outcomes [29, 30].

This is the first meta-analysis to assess AUC and VIKI; however, several limitations should be noted. First, due to the relatively wide range of reported AUC thresholds for nephrotoxicity (550–700 mg × hour/L), we decided to use an average of 650 mg × hour/L as a threshold for VIKI as supported by recent prospective study [28]. Second, all studies included in our analysis were observational studies. Observational studies can exhibit selection bias and various types of confounding. The identified studies, however, were the only published studies to

date that investigated AUC's impact on VIKI. Third, due to inconsistency of reported parameters in included studies, we were not able to assess a link between reported incidence of nephrotoxicity and severity of illness, concomitant nephrotoxins, or other relevant covariates. Fourth, all studies included in the analysis defined AKI using the vancomycin guidelines' definition of VIKI (an increase in serum creatinine of ≥0.5 mg/L or a 50% increase from baseline on 2 or more consecutive measurements), which is the second level of toxicity in both the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease and Acute Kidney Injury Network criteria. Due to the retrospective nature of the analysis, we had no control over the definitions used. Last, after compilation of all studies for inclusion using our predefined methodologic approach, we became aware that a new study assessing vancomycin AUC monitoring strategy had been published that we could not include in our analysis [38]. The goal of the study was to define AUC thresholds for efficacy and toxicity in patients with MRSA bacteremia after implementing 2-level AUC estimation methods. Using CART analysis, the authors reported a higher incidence of AKI with AUCs ≥710 mg × 24 hour/L. These results are concordant with our findings and would have been similarly classified with our definition (ie AUC of ~650 ± 100 mg × hour/L). It is notable that only 6 patients experienced nephrotoxicity, and the sensitivity of the cutpoint of 710 mg × hour/L for predicting nephrotoxicity was only 33% (ie, n = 2/6). The specificity (which is more relevant to preventing nephrotoxicity) was 97.5% (n = 39/40). Thus, this study is in agreement with our proposed threshold that urges caution at AUC of approximately 650 ± 100 mg × 24 hour/L.

CONCLUSIONS

In conclusion, our meta-analysis suggests that VIKI is associated with higher vancomycin exposures (AUC approximately ≥650 mg × 24 hour/L). However, since this cutoff was driven by only one prospective trial, further investigations in larger scales of patients are warranted and more work is needed to define the continuum of exposures as they relate to AKI. Our findings also suggest that AUC-monitoring strategies may be the preferred method for vancomycin therapeutic drug monitoring. Large randomized clinical trials, though, are ultimately needed to confirm these results.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

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