Development and Validation of a Risk Prediction Model of Vancomycin-Associated Nephrotoxicity in Elderly Patients: A Pilot Study

Chen Pan1,†, Aiping Wen†,†, Xingang Li1, Dandan Li1, Yang Zhang1, Yin Liao1, Yue Ren1 and Su Shen1,*

This exploratory study aimed to develop a risk prediction model of vancomycin-associated nephrotoxicity (VANT) in elderly patients. Clinical information of elderly patients who received vancomycin therapy from January 2016 to June 2018 was retrieved. A total of 255 patients were included in this study. Univariate analysis and multivariable logistic regression analysis revealed that vancomycin trough concentration ≥ 20 mg/L (odds ratio (OR) = 3.009; 95% confidence interval (CI) 1.345–6.732), surgery (OR = 3.357; 95% CI 1.309–8.605), the Charlson Comorbidities Index ≥ 4 points (OR = 2.604; 95% CI 1.172–5.787), concomitant use of cardiotonic drug (OR = 3.283; 95% CI 1.340–8.042), plasma volume expander (OR = 3.459; 95% CI 1.428–8.382), and piperacillin/tazobactam (OR = 2.547; 95% CI 1.680–6.007) were risk factors for VANT in elderly patients. Furthermore, a VANT risk prediction model was developed, which had good discriminative power and was well-calibrated.

Vancomycin is used to treat methicillin-resistant Staphylococcus aureus (MRSA) infections.1,2 Vancomycin-associated nephrotoxicity (VANT)3 is a common adverse drug reaction, and is linked to the need for renal replacement therapy, prolonged hospitalization, higher healthcare costs, and increased mortality.4 Elderly patients are more likely to develop VANT due to multiple illnesses and complicated medications. The incidence of VANT in the general adult patients was 4.7–15.4%,8–11 whereas the rate was 15.8–29% in elderly patients.6,12 With the aging of our society, VANT in elderly patients is worthy of more attention.12

Previous studies indicate that age,7 mechanical ventilation,12 intensive care unit (ICU) admittance,13 vancomycin trough concentration,9,14–17 dose,15 length of therapy,8,17 infusion method (continuous or intermittent infusions),18,19 cirrhosis,14 hypertension,20 hyperuricemia,12 shock,6 heart failure,6 concomitant medications, vasopressor drugs,16,17 aminoglycosides,9,21 contrast agents,22,23 piperacillin/tazobactam (PTZ),24,25 furosemide,3,11 amphotericin B,26 and the Acute Physiology and Chronic Health Evaluation II (APACHE-II)5,12,27 are risk factors associated with VANT. However, only two studies reported VANT risk factors in elderly patients.6,12 Additionally, there are few reports on developing risk prediction models of VANT in elderly patients. Therefore, we attempted to explore clinical predictors of VANT to construct a risk prediction model of VANT in elderly patients.

†Chen Pan and Aiping Wen contributed equally to this work.

1Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, China. *Correspondence: Su Shen (shensu11022000@163.com)

Received: September 5, 2019; accepted: October 24, 2019. doi:10.1111/cts.12731
METHODS

Study population
This was a retrospective study performed at Beijing Friendship Hospital, Capital Medical University. Inpatients treated with vancomycin from January 2016 to June 2018 were recruited. The inclusion criteria were: (i) ≥ 60 years old; and (ii) receiving vancomycin therapeutic drug monitoring (TDM). Patients were excluded if: (i) receiving vancomycin therapy < 48 hour; (ii) stage 5 chronic kidney disease; (iii) receiving renal replacement therapy; and (iv) lack of enough serum creatinine (Scr) information to assess VANT. This study was approved by the ethics committee of Beijing Friendship Hospital (Reference No. 2019-P2-168-01).

Data extraction
Patients’ clinical parameters were extracted mainly based on previous studies.\(^3\) Data extracted from the hospital's electronic database included sex, weight, date of birth, admission dates and diagnosis, serum lactate, serum creatinine and serum albumin, the start and stop dates of vancomycin, vancomycin dosage and interval, and concomitant medications, including angiotensin converting enzyme inhibitors, angiotensin receptor blocker, aminoglycoside, carbapenem, quinolones, antibiotic drugs, diuretics, immunosuppressant, proton pump inhibitors, cardiotonic drugs, vasopressor, plasma volume expander, contrast agent, fluconazole, voriconazole, caspofungin, amphotericin B, PTZ, mannitol, sulfamethoxazole, and aescinate. Other information extracted included if patients were transferred to the ICU, had surgery, and/or mechanical ventilation while on vancomycin therapy. Charlson Comorbidities Index (CCI) was calculated based on admission diagnosis.\(^2\) All vancomycin trough concentrations were recorded. For patients who developed VANT, only trough concentrations, serum lactate, serum creatinine, and serum albumin collected before the occurrence of VANT were analyzed. If multiple vancomycin trough serum concentrations were measured, the maximum concentration was chosen for analysis.\(^1^)\n
Dosing of vancomycin
Local vancomycin dosing protocol is 0.5 g q8h for elderly patients with intermittent infusion at rate of 500 mg/hour. Vancomycin trough level is measured for TDM, with blood sample taken 30 minutes before the next dose. TDM is conducted 48 hours after vancomycin therapy or dose adjustment. Clinicians adjust vancomycin dose based on infection parameters, adverse reactions, and the results of TDM.

Definition of VANT
VANT was defined as acute kidney injury that occurred during vancomycin therapy or within 2 days of discontinuing of vancomycin. Acute kidney injury was selected as the major screening criterion based on the Kidney Disease: Improving Global Outcomes definition: an increase in Scr by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours or increase in Scr to ≥ 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days.\(^2^)\n
Data analysis
By simple randomization, all eligible patients were randomized into a train set and a validation set (4:1 ratio). Based on the train data set, a risk model and a risk score system were developed sequentially. Normally distributed continuous variables were expressed as the mean ± SD, and groups were compared using the independent t-test. Non-normally distributed continuous variables were presented as the median (interquartile range), and groups were compared using the rank-sum test. Categorical variables were expressed as number (percentage) and analyzed using the χ² test or Fisher’s exact test.

For a clearer expression, age was divided into 60–79 and ≥ 80 years, serum albumin valley was divided into < 25 and ≥ 25 g/L, CCI score was divided into < 4 and ≥ 4 points, the vancomycin trough concentration was divided into 4 groups: < 10 mg/L, 10–15 mg/L, 15–20 mg/L, and ≥ 20 mg/L.

Variables that were significant at P < 0.1 in the univariate analyses and of clinical importance were entered into a stepwise multivariable logistic regression model. Variables retained in the final model were used to construct the risk model. According to the multivariable logistic regression model, a risk score was developed. To evaluate the discrimination of the risk model, receiver operating characteristic (ROC) curves were constructed, and area under the curve (AUC) was calculated. The calibration of the risk model was evaluated by the Hosmer-Lemeshow test and calibration plot. All data analyses were performed using SAS version 9.4 (SAS Institute). A two-sided P < 0.05 was considered significant.

RESULTS

Basic information
As shown in Figure 1, of the 2,008 patients who received vancomycin, 255 were included in the study. The most common reason for patient exclusion was stage 5 chronic kidney disease (68.25%; 86/126). Of the 1,110 elderly inpatients who received vancomycin, 34.32% (381/1110) received vancomycin TDM. Among the 255 patients, 63 (24.71%) experienced VANT. Forty-seven of the 204 patients (23.04%) experienced VANT in the train set, whereas 16 of 51 (31%) experienced VANT in the validation set. All factors considered except sex and age were balanced between the train and validation sets (Table 1).

Univariate analysis
A comparison of patient characteristics in the train set was shown in Table S1. A total of 15 variables were significant (P < 0.1) in the univariate analyses (Table 2). After excluding concomitant immunosuppressant (as the number of cases was too low), 14 variables finally entered into multivariable logistic regression analysis, including: age, surgery, ICU admittance, mechanical ventilation, serum albumin valley, CCI score, respiratory failure, sepsis, trough concentration, aminoglycoside, cardiotonic drug, vasopressor, plasma volume expander, and PTZ.
The vancomycin trough concentration was originally divided into 4 groups: < 10 mg/L, 10–15 mg/L, 15–20 mg/L, and ≥ 20 mg/L. Univariate logistic regression analysis showed that VANT was associated with vancomycin trough concentration ≥ 20 mg/L (odds ratio (OR) = 3.450; 95% confidence interval (CI) 1.146–10.390; Table S2). Hence, vancomycin trough concentration was divided into two groups of < 20 or ≥ 20 mg/L in the multivariable logistic regression analysis.

**Multivariable logistic regression model**

Multiple logistic regression analysis revealed that vancomycin trough concentration ≥ 20 mg/L (OR = 3.009; 95% CI 1.345–6.732), surgery (OR = 3.357; 95% CI 1.309–8.605), CCI score ≥ 4 (OR = 2.604; 95% CI 1.172–5.787), concomitant cardiotonic drug (OR = 3.283; 95% CI 1.340–8.042), plasma volume expander (OR = 3.459; 95% CI 1.428–8.382), and PTZ (OR = 2.547; 95% CI 1.680–6.007) were risk factors for VANT (Table 3). On the basis of a multiple logistic regression model, a risk VANT prediction model in elderly patients was constructed:

\[
\text{logit}(P) = -5.3349 + 1.2109 \times \text{surgery} + 1.0116 \times \text{vancomycin trough concentration} + 0.9572 \times \text{CCI} + 1.1887 \times \text{cardiotonic drug} + 1.2410 \times \text{plasma volume expander} + 0.9350 \times \text{PTZ}
\]

(1)

where surgery, yes = 1, no = 0; vancomycin trough concentration, < 20 mg/L = 1 and ≥ 20 mg/L = 2; CCI score, < 4 = 1 and ≥ 4 = 2; cardiotonic drug, yes = 1, no = 0; plasma volume expander, yes = 1, no = 0; and PTZ, yes = 1, no = 0.

In the train set, the risk model had excellent discriminative power, with the AUC of 0.8278 (95% CI 0.7577–0.8979) and was well-calibrated with the Hosmer-Lemeshow $\chi^2$ statistic of 1.4791 ($P = 0.9830$; Figure 2).

**Risk score development**

To facilitate the clinical application, each risk factor was assigned a risk score according to the VANT risk assessment model (Table 4). The total risk score ranged from 0 to 6, with corresponding predicted probabilities of VANT ranging from 3.64–91.16% (0, 3.64%; 1, 8.78%; 2, 19.68%; 3, 38.44%; 4, 61.39%; 5, 80.20%; and 6, 91.16%). The incidence of VANT by risk assignment was depicted in Figure S1. In the train set, the trend of higher risk score linking to a higher incidence of VANT was apparent.

The risk scores were categorized into three levels to enhance the clinical use of the risk score model. Three risk levels were provided: low-risk (score 0–2, VANT incidence 12.3%), moderate-risk (score 3–4, VANT incidence 63.2%), and high-risk (score 5–6, VANT incidence 75.0%). In the train set, the trend of higher risk level linking to a higher incidence of VANT was apparent (Figure S2).

**Model validation**

The VANT risk model demonstrated good discriminative power in the validation population, with AUC of 0.7357 (95% CI 0.5813–0.8901; Figure 2). The incidence of VANT in the validation set showed evident increasing trend across each score value (Figure S1). In the validation set, the incidence of VANT of the low-risk, moderate-risk, and high-risk levels were, respectively, 22.5%, 55.6%, and 100.0%, which
showed a noticeable trend of higher risk level linking to a higher incidence of VANT (Figure S2).

**DISCUSSION**

In this study, we found vancomycin trough concentration ≥ 20 mg/L, surgery, CCI score ≥ 4, concomitant cardiotonic drug, plasma volume expander, and PTZ were risk factors for VANT in elderly patients. Based on this, we developed and validated a risk prediction model for elderly patients. To the best of our knowledge, our study is the first to attempt to develop a risk prediction model of VANT in elderly patients.

Many studies not particularly for elderly patients report vancomycin trough concentration is an important risk factor for VANT, which is consistent with this study. The guideline recommends keeping trough levels of 10–15 mg/L in adult patients and 10–20 mg/L in adult patients with serious MRSA infections. However, the guideline does not explicate vancomycin trough concentration range for elderly patients. We made further efforts to assess vancomycin trough concentration by using a logistic regression analysis model to predict the probabilities of VANT. The predicted

---

**Table 1** Demographic and clinical data of the patients in the train and validation sets

| Variable | Train set (N = 204) | Validation set (N = 51) | P value |
|----------|---------------------|-------------------------|---------|
| Demographic characteristics | | | |
| Sex (male/female) | 143/61 | 25/26 | 0.0045 |
| Age (years) | 84.0 (75.0, 90.0) | 82.0 (73.0, 88.0) | 0.0619 |
| 60–79 n (%) | 64 (31.4%) | 44 (27%) | 0.0351 |
| ≥ 80 n (%) | 140 (68.6%) | 27 (53%) | |
| Surgery n (%) | 43 (21.1%) | 11 (22%) | 0.9389 |
| ICU admittance n (%) | 47 (23.0%) | 14 (28%) | 0.5089 |
| Mechanical ventilation n (%) | 53 (26.0%) | 13 (26%) | 0.9430 |
| Laboratory variables | | | |
| Baseline SCr (μmol/L)a | 74.9 (62.4, 91.5) | 70.5 (54.5, 103.6) | 0.9655 |
| Peak serum lactic acid (mmol/L)b | 2.5 (1.8, 3.3) | 2.5 (2.0, 3.5) | 0.9746 |
| Serum albumin valley (g/L) | 25.7 ± 4.67 | 25.5 ± 5.41 | 0.7959 |
| < 25 n (%) | 83 (40.7%) | 22 (44%) | 0.7504 |
| ≥ 25 n (%) | 121 (59.3%) | 29 (57%) | |
| Comorbidity | | | |
| CCI score | 3.0 (2.0, 5.0) | 3.0 (2.0, 5.0) | 0.6589 |
| < 4 n (%) | 123 (60.3%) | 32 (63%) | 0.7485 |
| ≥ 4 n (%) | 81 (39.7%) | 19 (37.3%) | |
| Vancomycin therapy | | | |
| Daily dose (g/day) | 1.5 (1.1, 1.9) | 1.3 (1.1, 1.9) | 0.7899 |
| < 1.5 n (%) | 105 (50.5%) | 50 (59%) | 0.4501 |
| 1.5–2 n (%) | 52 (25.5%) | 9 (18%) | |
| ≥ 2 n (%) | 49 (24.0%) | 12 (24%) | |
| Length of therapy (days) | 12.0 (8.0, 15.0) | 10.0 (7.0, 14.0) | 0.0077 |
| 2–5 n (%) | 6 (2.9%) | 3 (6%) | 0.4279 |
| 5–10 n (%) | 68 (33.3%) | 22 (43%) | |
| 10–15 n (%) | 69 (33.8%) | 16 (31%) | |
| 15–20 n (%) | 39 (19.1%) | 7 (14%) | |
| ≥ 20 n (%) | 22 (10.8%) | 3 (6%) | |
| Trough concentration (mg/L) | 16.1 (12.7, 20.7) | 16.8 (12.1, 26.0) | 0.5037 |
| < 10 n (%) | 28 (13.7%) | 5 (10%) | 0.4025 |
| 10–15 n (%) | 53 (26.0%) | 16 (31%) | |
| 15–20 n (%) | 67 (32.8%) | 12 (24%) | |
| ≥ 20 n (%) | 56 (27.5%) | 18 (35%) | |

CCI, Charlson Comorbidities Index; ICU, Intensive Care Unit; SCr, serum creatinine.

*Eleven patients lacked baseline SCr.

Five patients lacked peak serum lactic acid.

---

**Table 2** Association of characteristics and VANT (train set, univariate analysis, P < 0.1)

| Variable | VANT (N = 47) | NO-VANT (N = 157) | P value |
|----------|-------------|------------------|---------|
| Demographic characteristics | | | |
| Age (years) | 80.0 (69.0, 87.0) | 86.0 (79.0, 90.0) | 0.0014 |
| 60–79 n (%) | 22 (47%) | 25 (15.3%) | 0.0093 |
| ≥ 80 n (%) | 25 (53%) | 115 (73.2%) | |
| Surgery n (%) | 20 (43%) | 23 (14.6%) | < 0.0001 |
| ICU admittance n (%) | 21 (45%) | 26 (16.6%) | < 0.0001 |
| Mechanical ventilation n (%) | 23 (49%) | 30 (19.1%) | < 0.0001 |
| Laboratory variables | | | |
| Serum albumin valley (g/L) | 23.0 ± 4.89 | 26.5 ± 4.30 | < 0.0001 |
| < 10 n (%) | 30 (64%) | 53 (33.8%) | 0.0002 |
| ≥ 25 n (%) | 17 (36%) | 104 (66.2%) | |
| Comorbidity | | | |
| CCI score | 4.0 (2.0, 5.0) | 3.0 (2.0, 4.0) | 0.0493 |
| < 4 n (%) | 20 (43%) | 103 (65.6%) | 0.0046 |
| ≥ 4 n (%) | 27 (57%) | 54 (34.4%) | |
| Respiratory failure n (%) | 18 (38%) | 38 (24.2%) | 0.0575 |
| Sepsis n (%) | 20 (43%) | 37 (23.6%) | 0.0109 |
| Vancomycin therapy | | | |
| Trough concentration (mg/L) | 20.1 (15.4, 28.0) | 15.5 (12.2, 18.8) | 0.0001 |
| < 10 n (%) | 5 (11%) | 23 (14.6%) | 0.0003 |
| 10–15 n (%) | 5 (11%) | 48 (30.6%) | |
| 15–20 n (%) | 13 (28%) | 54 (34.4%) | |
| ≥ 20 n (%) | 24 (51%) | 32 (20.4%) | |
| Concomitant drugs | | | |
| Aminoglycoside n (%) | 7 (15%) | 7 (4.5%) | 0.0208 |
| Cardiotonic drug n (%) | 18 (38%) | 20 (12.7%) | < 0.0001 |
| Immunosuppressant n (%) | 4 (9%) | 3 (1.9%) | 0.0507 |
| Vasopressor n (%) | 22 (47%) | 25 (15.9%) | < 0.0001 |
| Plasma volume expander n (%) | 24 (51%) | 23 (14.6%) | < 0.0001 |
| PTZ n (%) | 16 (34%) | 34 (21.7%) | < 0.0001 |

CCI, Charlson Comorbidities Index; ICU, intensive care unit; PTZ, piperacillin/tazobactam; VANT, vancomycin-associated nephrotoxicity.
probability curve showed that the probability of VANT risk increased as the vancomycin trough concentration increased. Receiver operating characteristic analysis identified 18.1 mg/L as the vancomycin trough concentration with the greatest sensitivity and specificity for VANT in elderly patients (Figures S3 and S4). This result shows that high trough concentration recommended by the guideline might increase the incidence of VANT for elderly patients with serious MRSA infections. The guideline recommends that TDM should be performed in elderly patients, whereas the rate of TDM in our study was relatively low (32.5%). However, the latest guideline recommended AUC instead of trough concentration as the pharmacokinetic/pharmacodynamic marker of vancomycin, which may reduce the adverse impact of trough concentration on VANT.

CCI has been widely utilized to measure the burden of disease and predict mortality. Many elderly patients have multiple comorbidities, therefore, we tried to explore the effect of CCI to VANT in elderly patients. This study showed...
that CCI was a risk factor for VANT, which indicates that elderly patients with poor physical condition are more likely to develop VANT. This is the first study to explore the effect of CCI to VANT in elderly patients. We also found surgery was a risk factor, which is consistent with the result of CCI.

Elderly patients usually take various concomitant medications.22 Thirteen kinds and eight varieties of drugs which may cause nephrotoxicity or affect renal function were included, and the results of our study demonstrated that concomitant cardiotonic drugs and plasma volume expander were risk factors for VANT in elderly patients. These two categories of medication are for patients with heart failure and circulatory shock, respectively. The results suggest that the cardiac function and circulation of the patients would affect the occurrence of VANT, which should be handled before vancomycin therapy. PTZ was extensively studied in previous studies and proved to be an important risk factor for VANT.24,25 We found similar results in elderly patients. PTZ might lead to vancomycin's accumulation within nephron by decreasing its clearance.

Our study developed and validated a risk prediction model of VANT for elderly patients, and the risk scores were divided into three levels of low, moderate, and high-risk groups for assessing VANT risk in elderly patients. This provided a relatively practical tool for clinicians to identify patients with high-risk VANT for close monitoring. For these patients, prompt measures could be taken, such as reducing the dosage of vancomycin or ceasing vancomycin therapy to reduce its trough concentration, monitoring the patient's renal function, and avoiding combined use of other nephrotoxic drugs.22,23

Two limitations should be addressed. First, this was a retrospective single-center study, and the validation was conducted with retrospective data. This might have generated biases and the results are subjected to future prospective multicenter studies. Second, the sample size was relatively small to develop a classical risk prediction model, and the validation data sets were not independent samples, which may lead to the instability of our model. However, the results of our model were inspiring, which had good discriminative power. Therefore, we want to share our exploratory results and hope our model can be further validated.

Supporting Information. Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

Table S1. Association of characteristics and VANT (train set, univariate analysis).

Table S2. Univariate logistic regression analysis of vancomycin trough concentration (train set, n = 204).

Figure S1. Incidence of VANT with increasing risk score in the train set and the validation set. The individual risk score was calculated as the sum of each weighted score for the six predictive factors of VANT. Solid bars = train set; open bars = validation set.

Figure S2. Incidence of VANT according to the three risk classes in the train set and the validation set. Solid bars = train set; open bars = validation set.

Figure S3. Logistic regression analysis model of the relationship between vancomycin trough concentrations and the predicted probabilities of VANT associated with these concentrations.

Figure S4. ROC curve to evaluate the predictive value of vancomycin trough concentration to VANT using the train sets. ROC curves, receiver operating characteristic curves.

Data Set S1. Example model code and data sets of risk prediction model of VANT in elderly patients.

Acknowledgments. The authors thank Yanlong Li and Yang Li for helping in analyzing the data.

Funding. No funding was received for this work.

Conflicts of Interest. All authors declared no competing interests for this work.

Author Contributions. C.P., A.W., and S.S. wrote the manuscript. C.P., A.W., and S.S. designed the research. C.P., A.W., X.L., D.L., Y.Z., Y.L., Y.R., and S.S. performed the research. C.P., A.W., and S.S. analyzed the data.

1. Liu, C. et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin. Infect. Dis. 3, 818–855 (2011).
2. van Hal, S.J., Paterson, D.L. & Lodise, T.P. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob. Agents Chemother. 2, 734–744 (2013).
3. Imai, S. et al. Construction of a risk prediction model of vancomycin-associated nephrotoxicity to be used at the time of initial therapeutic drug monitoring: a data mining analysis using a decision tree model. J. Eval. Clin. Pract. 1, 163–170 (1999).
4. Ricci, Z., Cruz, D. & Ronco, C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int. 5, 538–546 (2008).
5. Kane-Gill, S.L. et al. Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. Am. J. Kidney Dis. 6, 860–869 (2015).
6. Liu, Y. et al. Retrospective analysis of vancomycin nephrotoxicity in elderly Chinese patients. Pharmacology 95, 279–284 (2015).
7. Hall, R.G. 2nd et al. Empiric guideline-recommended weight-based vancomycin dosing and mortality in methicillin-resistant Staphylococcus aureus bacteremia: a retrospective cohort study. BMC Infect. Dis. 12, 104 (2012).
8. Rybak, M.J., Albrecht, L.M., Boike, S.C. & Chandrasekar, P.H. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. J. Antimicrob. Chemother. 4, 679–687 (1999).
9. Cano, E.L. et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. Clin. Ther. 1, 149–157 (2012).
10. Lodise, T.P., Patel, N., Lomaestro, B.M., Rodvold, K.A. & Drusano, G.L. Relationship between initial vancomycin concentration–time profile and nephrotoxicity among hospitalized patients. Clin. Infect. Dis. 4, 507–514 (2009).
11. McKamy, S. et al. Incidence and risk factors influencing the development of vancomycin nephrotoxicity in children. J. Pediatr. 3, 422–426 (2011).
12. Pan, K.M. et al. Vancomycin-induced acute kidney injury in elderly Chinese patients: a single-centre cross-sectional study. Br. J. Clin. Pharmacol. 8, 1706–1718 (2018).
13. Park, S.J. et al. Evaluation of risk factors for vancomycin-induced nephrotoxicity. Int. J. Clin. Pharm. 5, 1328–1334 (2018).
14. Lacave, G. et al. Incidence and risk factors of acute kidney injury associated with continuous intravenous high–dose vancomycin in critically ill patients: a retrospective cohort study. Medicine (Baltimore) 7, e0023 (2017).
15. Dong, M.H. et al. Evaluation of body weight-based vancomycin therapy and the incidence of nephrotoxicity: a retrospective study in the northwest of China. Int. J. Infect. Dis. 37, 125–128 (2015).
16. Chuma, M. et al. Relationship between initial vancomycin trough levels and early-onset vancomycin–associated nephrotoxicity in critically ill patients. Ther. Drug Monit. 1, 109–114 (2018).
17. Hanrahan, T.P. et al. Vancomycin-associated nephrotoxicity in the critically ill: a retrospective multivariate regression analysis. Crit. Care Med. 12, 2527–2536 (2014).
18. Hong, L.T. et al. Continuous infusion vs intermittent vancomycin in neurosurgical intensive care unit patients. J. Crit. Care 30, 1153.e1–1153.e6 (2015).
19. Bissell, B.D., Riggi, G. & Morrison, C. Evaluation of continuous infusion vancomycin administration in a critically ill trauma population. J. Intensive Care Med. 35, 570–575 (2020).
20. Cappelletty, D., Jablonski, A. & Jung, R. Risk factors for acute kidney injury in adult patients receiving vancomycin. Clin. Drug Investig. 3, 189–193 (2014).
21. Hanrahan, T.P. et al. Factors associated with vancomycin nephrotoxicity in the critically ill. Anaesth. Intensive Care. 5, 594–599 (2015).
22. Prabaker, K.K., Tran, T.P., Pratummas, T., Goetz, M.B. & Graber, C.J. Elevated vancomycin trough is not associated with nephrotoxicity among inpatient veterans. J. Hosp. Med. 2, 91–97 (2012).
23. Rostas, S.E., Kubiak, D.W. & Calderwood, M.S. High-dose intravenous vancomycin therapy and the risk of nephrotoxicity. Clin. Ther. 7, 1098–1101 (2014).
24. Luther, M.K. et al. Vancomycin plus piperacillin–tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. Crit. Care Med. 1, 12–20 (2018).
25. Hammond, D.A. et al. Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. Clin. Infect. Dis. 5, 666–674 (2017).
26. Rocha, P.N. et al. Incidence, predictors, and impact on hospital mortality of amphotericin B nephrotoxicity defined using newer acute kidney injury diagnostic criteria. Antimicrob. Agents Chemother. B, 4758–4769 (2015).
27. Huang, M., Wu, H., Zhou, J., Xu, M. & Zhou, S. Efficacy of vancomycin on gram-positive bacterial infection in elderly critical patients and risk factors associated with nephrotoxicity. Arch. Iran Med. 8, 349–355 (2018).
28. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 5, 373–383 (1987).
29. James, M. et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am. J. Kidney Dis. 5, 673–685 (2013).
30. Ye, Z.K. et al. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. J. Antimicrob. Chemother. 11, 3020–3025 (2016).
31. Kostek, O. et al. Is the Charlson Comorbidity Index a prognostic indicator for toxicity and mortality in elderly patients with locally advanced rectal cancer? Arch. Iran Med. 5, 236–241 (2019).
32. Tangisuran, B. et al. Development and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton Adverse Drug Reactions Risk (BADRI) model. PLoS One 10, e111254 (2014).
33. Watkins, R.R. & Deresinski, S. Increasing evidence of the nephrotoxicity of piperacillin/tazobactam and vancomycin combination therapy—what is the clinician to do? Clin. Infect. Dis. 12, 2137–2143 (2017).