Incidence Evaluation of Acute Kidney Injury and Pharmacoeconomic Analysis Among Critically Ill Patients With Use of Antipseudomonal β-Lactams and Vancomycin

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Research

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Abstract

Background: Whether vancomycin (VAN) plus piperacillin-tazobactam (PTZ) could increase the risk of acute kidney injury (AKI) is still controversial in critically ill patients. The purpose of this study was to compare the risk of developing AKI and risk of developing AKI and treatment cost among this population receiving VAN/PTZ to a matched group receiving VAN/other antipseudomonal β-lactams.

Methods: This multicenter, retrospective, matched study included 700 critically ill patients who received ≥48 hours of VAN/PTZ or VAN/other antipseudomonal β-lactams. The risk of developing AKI was compared between these two combination therapies using propensity-adjusted analysis. Furthermore, a pharmacoeconomic decision-analytic model was performed.

Results: According to three AKI-defined criteria, VAN/PTZ was associated with significantly higher incidence of than VAN/other antipseudomonal β-lactams (all $P < 0.001$). In multivariate analysis, regardless of any VAN/other antipseudomonal β-lactams, VAN/PTZ was an independent predictor for stage 2 or 3 AKI. In the empiric treatment, the incremental cost-effectiveness ratios per additional nephrotoxic episode of 1147.35$, 1845.11$, and 3989.95$ were found for VAN/PTZ relative to, vancomycin plus imipenem-cilastatin, vancomycin plus meropenem, and vancomycin plus cefoperazone-sulbactam, respectively.

Conclusion: In critically ill patients, VAN/PTZ was associated with both higher AKI risk and treatment cost when considering AKI occurence compared to VAN/other antipseudomonal β-lactams.

Trial registration: retrospectively registered, ClinicalTrials.gov number: NCT03776409.

Introduction

Critically ill patients usually present with bacteremia and with hospital-acquired infections, thus empirical antimicrobial therapy is inevitable. Vancomycin in combination with antipseudomonal β-lactams (VAN/BL) is a common method in clinical practice (1).

Traditionally, hospitals have selected piperacillin-tazobactam (PTZ) or other β-lactam as the “workhorse” antipseudomonal antibiotics based on institutional susceptibility trends, acquisition costs, and other prescription considerations (2, 3). Nevertheless, recent studies show that an increased risk of acute kidney injury (AKI) is found for vancomycin plus piperacillin-tazobactam (VAN/PTZ) (4–7). Moreover, AKI induced by VAN/PTZ may lead to an increase in mortality, hospital duration, and treatment costs. Although current literature supports the association of AKI in non-critically ill patients, limited studies of critically ill patients have failed to demonstrate that VAN/PTZ increases the risk of AKI. Only one study has shown such association in critically ill patients (8). However, this large sample study includes severe renal insufficiency patients (baseline estimated glomerular filtration rate [eGFR] level of ≤ 30 mL/min), which might increase the bias of identifying the nephrotoxicity of treatment. Another study that evaluated the brief empiric use of VAN/PTZ therapy (< 72 hours) suggests that the use of VAN/PTZ therapy in critically ill patients does not confer a risk of AKI (5). Nevertheless, previous studies showed that duration of VAN/PTZ usually exceeds 72 hours and the onset of drug-induced AKI typically occurs after about 4–8 days of therapy in clinical practice

(9–11). Therefore, it is necessary to evaluate the the safety of combination therapy on combination duration of ≥ 48 hours.

Given the controversy results of previous studies, this study is designed to explore whether the critically ill patients receiving VAN/PTZ have a greater risk of AKI compared with patients receiving VAN/BL. A pharmacoeconomic analysis was to investigate the difference among VAN/PTZ and VAN plus cefoperazone-sulbactam (VAN/CPZ-SBT) or VAN plus meropenem (VAN/MEM) or VAN plus imipenem-cisastatin (VAN/IPM-CIS) of treatment costs in this population using clinical safety data generated by the cohort study, epidemiological data, and local medical data.

Materials And Methods

Study design

This was a multicenter, retrospective study. Eligible patients were adults hospitalized in any of the ICUs at 16 medical centers between January 1 2008 and December 31 2018. For patients admitted on multiple times during the study time, the last admission was used. This study was approved by all medical centers with a waiver of informed consent. This study has been registered with the Clinical Trials Registration Center (ClinicalTrials.gov) (NCT03776409).

Patients selection

Patients were eligible if they 1) were ≥ 18 years, 2) were admitted to the any of the ICUs, 3) received VAN/β-lactams (PTZ, CPZ-SBT, ceftazidime, cefepime, MEM, IPM-CIS, biapenem) combination therapy ≥ 48 hours.

Patients were excluded if they 1) received > 1 antipseudomonal β-lactams during vancomycin treatment, 2) developed AKI before concomitant antibiotic therapy initiation, 3) had end-stage renal disease, 4) died within 48 hours of combination therapy initiation, 5) were pregnant.

Data Collection

Data were collected using an electronic recording form using the Research Electronic Data Capture (REDCap) software (12), which was developed by the Department of Medicine of the University of Padova, Italy (see details of study oversight in Additional file). Data were extracted from electronic records included demographic information, comorbidities, APACHE II score, SOFA score, mechanical ventilation, infection types, AKI risk scores, and microbiological data. Antibiotic therapy covariates were collected including dose and duration of treatment (see details of data collection in Additional file).

Outcomes

The primary outcomes were the incidence of any AKI defined by the three definitions (the Acute Kidney Injury Network [AKIN] criteria (13), the Risk-Injury-Failure-Loss-End Stage Renal Disease [RIFLE] criteria (14) and vancomycin consensus guideline (15)) and the incidence of stage 2 or 3 AKI defined by the AKIN criteria. The occurrence of AKI was assessed beginning 24 hours after initiation of combination therapy. Follow-up

continued until 7 days after 1 or both antibiotics in the combination were discontinued (see Additional file Table S.1.).

The secondary outcomes included the ICU length of stay, time to the occurrence of AKI, duration of AKI, the return of the renal function to baseline by hospital discharge, new renal replacement therapy (RRT) requirement, and microbiological response.

Statistical analysis

For the primary outcome of AKI defined by the AKIN criteria, we determined a sample size of at least 149 patients in each group (VAN/PTZ vs VAN/BL) to achieve a statistical power of 80% using an α of 0.05 based on a previous study (8) which reported the incidence of VAN/PTZ and VAN/BL (39.3% vs 24.2%).

For categorical data, the Pearson χ^2 test or Fisher's exact test was used. For continuous data, the Student's t-test and Wilcoxon rank-sum test were used. To control for non-randomized potential bias, a propensity score-matched analysis was conducted. Patients were divided into two combination therapy groups (VAN/PTZ and VAN/BL groups). A 1:3 ratio with a caliper length of 0.2 SDs was used to match the patients in the VAN/PTZ group and those in VAN/BL group. The matching was performed based on covariates with significant differences in the baseline characteristics between the two groups (Table 1). In the subgroup analysis, we selected the top three combination treatments to evaluate the risk of AKI and perform pharmacoeconomic analysis. The patients in the VAN/PTZ group were matched to VAN/CPZ-SBT, VAN/MEM, and VAN/IPM-CIS groups in a 1:1 ratio. To evaluate risk factors of AKI between VAN/PTZ and VAN/BL groups, all variables with a P value < 0.2 in the bivariate matched analysis were included in multivariate analysis. For the secondary outcome of time to AKI, comparisons were made with the Kaplan-Meier curve and the log-rank test. We used SPSS 22.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. $P < 0.05$ was considered statistically significant. If a covariate was completely missing for an individual, the population median was used.

Table 1
Baseline Characteristics of Cohort Comparing Patients Receiving VAN/PTZ to Patients Receiving VAN/antipseudomonal β-lactams

Patient baseline characteristic	Unmatched			Matched		
	VAN/PTZ (n = 154)	VAN/other antipseudomonal β-lactams [1] (n = 546)	*P* value	VAN/PTZ (n = 148)	VAN/other antipseudomonal β-lactams (n = 337)	*P* value
Age(years), mean ± SD	58 ± 16	60 ± 17	0.148	59 ± 16	59 ± 17	0.853
Male sex (N, %)	88 (57.1)	362 (66.3)	**0.036**	88 (59.4)	215 (63.8)	0.34
Body weight(kg), mean ± SD	60.6 ± 3.2	60.9 ± 4.0	0.500	60.7 ± 3.2	61.0 ± 4.3	0.391
APACHE II score, mean ± SD	12 ± 3	13 ± 4	**0.006**	12 ± 3	13 ± 3	0.209
SOFA score, mean ± SD	6 ± 1	6 ± 1	0.164	6 ± 1	6 ± 1	0.216
AKI risk prediction score at antibiotic initiation (N, % of each component)[2], mean ± SD	3.8 ± 2.5	4.8 ± 2.5	**< 0.001**	3.9 ± 2.5	4.2 ± 2.4	0.371
Chronic kidney disease	17 (11.0)	44 (8.1)	0.247	17 (11.5)	26 (7.7)	0.183
Chronic liver disease	18 (11.7)	45 (8.2)	0.187	18 (12.2)	25 (7.4)	0.093

Statistically signifcant values are shown in bold.

VAN: Vancomycin; PTZ: Piperacillin-Tazobactam; SD: Stand Deviation; APACHE: Acute Physiology and Chronic Health Evaluation score; SOFA: Sequential Organ Failure Assessment score; AKI, Acute Kidney Injury; IQR: Interquartile Range; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; WBC: White Blood Cell.

[1]: Other beta-lactams included meropenem (182/546, 33.4%), cefoperazone/sulbactam (158/546, 28.9%), imipenem/cisastatin (114/546, 20.9%), ceftriaxone (44/546, 8.1%), biapenem (27/546, 4.9%), ceftazidime (14/546, 2.6%), cefepime (4/546, 0.7%), latamoxef (3/546, 0.6%).

[2]: This score assigns points for increasing risk related to chronic conditions (chronic kidney disease, chronic liver disease, congestive heart failure, hypertension, atherosclerotic cardiovascular disease) and acute disease states and exposures (pH ≤ 7.3, nephrotoxin exposure, sepsis [defined in this study by Sepsis-3 criteria], mechanical ventilation requirement and anemia). Scores range from 0 to 21 with higher scores indicating increased risk.

[3]: Nephrotoxin exposure was evaluated from 7 days prior to hospital admission to 48 hours after intensive care unit admission.

Patient baseline characteristic	Unmatched			Matched		
	VAN/PTZ (n = 154)	VAN/other antipseudomonal β-lactams [1] (n = 546)	*P* value	VAN/PTZ (n = 148)	VAN/other antipseudomonal β-lactams (n = 337)	*P* value
Congestive heart failure	26 (16.8)	87 (15.9)	0.777	26 (17.6)	51 (15.1)	0.511
Hypertension	54 (35.1)	228 (56.0)	0.135	54 (36.5)	138 (40.9)	0.34
Atherosclerotic cardiovascular disease	17(11)	78(14.3)	0.587	16 (10.8)	42 (13.3)	0.798
pH ≤ 7.3	9 (5.8)	39(7.1)	0.573	8 (5.4)	24 (7.1)	0.477
Mechanical ventilation	77 (50.0)	259 (47.4)	0.574	77 (52.0)	150 (44.5)	0.137
Anemia (hemoglobin < 9 g/dL)	32 (20.8)	120 (21.9)	0.750	32 (21.6)	87 (25.8)	0.313
Sepsis	19 (12.3)	103 (18.8)	0.059	18 (12.2)	59 (17.5)	0.134
Concomitant nephrotoxins[3] (N, %)						
Median number of nephrotoxins (IQR)	0 (0–0)	0 (0–1)	**< 0.001**	0 (0–0)	0 (0–1)	**0.017**
Vasopressors	6 (3.9)	84 (15.4)	**< 0.001**	6 (4.1)	36 (10.7)	**0.016**

Statistically signifcant values are shown in bold.

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Patient baseline characteristic	Unmatched			Matched		
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Aminoglycoside	2 (1.3)	25 (4.6)	0.062	2 (1.3)	12 (3.6)	0.294
Diuretics	20 (13.0)	83 (15.2)	0.493	20 (13.5)	36 (10.7)	0.377
Intravenous contrast	4 (2.6)	9 (1.6)	0.665	4 (2.7)	2 (0.6)	0.138
Nonsteroidal anti-inflammatory drugs	5 (3.2)	33 (6.0)	0.176	5 (3.4)	13 (3.8)	0.792
Comorbid conditions (N, %)						
Diabetes mellitus	28 (18.2)	98 (17.9)	0.947	28 (18.9)	60 (17.8)	0.783
Hypoproteinemia	81 (52.6)	149 (27.3)	**< 0.001**	78 (52.7)	92 (27.3)	**< 0.001**
Malignant solid tumor	22 (14.3)	38 (6.9)	**0.004**	22 (14.8)	27 (8.1)	**0.022**
Chronic obstructive pulmonary disease	12 (7.8)	54 (9.9)	0.431	12 (8.1)	38 (11.3)	0.285
Infection type (N, %)						

Statistically signifcant values are shown in bold.

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Pneumonia	108 (70.1)	400 (73.3)	0.442	105 (70.9)	254 (75.4)	0.28
Endocarditis	1 (0.6)	8 (14.6)	0.427	1 (0.7)	4 (1.2)	0.977
Central nervous system infection	20 (13.0)	66 (12.1)	0.764	20 (13.5)	38 (11.3)	0.494
Intraabdominal infection	17 (11.0)	29 (5.3)	**0.011**	17 (11.5)	19 (5.6)	**0.024**
Skin/soft tissue infection	2 (1.3)	11 (2.0)	0.808	2 (1.3)	4 (1.2)	1
Bone/joint infection	1 (0.6)	4 (0.7)	1	0 (0)	3 (0.9)	0.599
Urinary tract infection	9 (5.8)	22 (4.0)	0.334	9 (6.1)	14 (4.1)	0.363
Bacteremia	6 (3.9)	35 (6.4)	0.241	6 (4.1)	13 (3.8)	0.925
Other/unknown	11 (7.1)	8 (1.5)	**< 0.001**	11 (7.4)	6 (1.8)	**0.002**
Polymicrobial infection	17 (11.0)	49 (9.0)	0.439	17 (11.5)	26 (7.7)	0.183
Pathogens (N, %)						

Statistically signifcant values are shown in bold.

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Gram-positive bacteria	56 (36.4)	155 (28.4)	0.057	53 (35.8)	93 (27.6)	0.074
MRSA	12 (7.8)	37 (6.8)	0.663	10 (6.7)	20 (5.9)	0.737
MSSA	9 (5.8)	29 (5.3)	0.797	9 (6.1)	19 (5.6)	0.855
Gram-negative bacteria	37 (24.0)	130 (23.8)	0.956	34 (23.0)	80 (23.7)	0.838
Pseudomonas	4 (2.6)	27 (4.9)	0.211	3 (2.1)	16 (4.7)	0.153
Enterobacteriaceae	11 (7.1)	45 (8.2)	0.657	11 (7.4)	29 (8.6)	0.657
Initial vancomycin dose (mg) per 24 h [IQR]	2000 (1000–2000)	2000(1500–2000)	0.593	2000 (1000–2000)	2000 (1500–2000)	0.165
Baseline WBC, mean ± SD	10.75 ± 7.86	12.62 ± 11.6	**0.010**	10.79 ± 7.91	10.94 ± 6.1	0.257
Baseline serum creatinine, mean ± SD	62.3 ± 29.6	70.2 ± 43.1	**0.019**	62.8 ± 29.6	65.7 ± 38.5	0.418
Baseline creatinine clearance, mean ± SD	117.3 ± 38.6	104.3 ± 45.7	**0.024**	116.4 ± 37.8	113.5 ± 42.3	0.512

Statistically signifcant values are shown in bold.

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Days of vancomycin therapy [IQR]	7 (5–11)	6 (4–12)	0.269	7 (5–10)	6 (4–10)	0.264
Days of combination therapy [IQR]	5 (4–8)	6 (4–9)	0.339	5 (4–8)	6 (4–9)	0.619

Statistically signifcant values are shown in bold.

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Pharmacoeconomic analysis

We constructed a decision analysis model using TreeAge Pro 2011 (TreeAge Software, MA, USA) (Additional file Figure S.1.) from the healthcare system perspective. The AKI incidence of VAN/PTZ was weighted from multiple clinical studies (8, 16–18). The AKI incidence of VAN/PTZ and OR for developing AKI for VAN/CPZ-SBT, VAN/MEM, VAN/IPM-CIS versus VAN/PTZ as estimated in the multivariate analysis were employed to produce the respective probabilities for VAN/β-lactams. The costs of drug acquisition were obtained from the National Health and Family Planning Commission of the People's Republic of China (http://www.nhfpc.gov.cn). All costs were recorded in Chinese yuan and then converted into US dollars (exchange rate: 1 yuan = US$0.1398). The incremental cost effectiveness ratio (ICER) per nephrotoxic episode prevented was calculated to compare the performance of combination therapy. Additionally, one-way sensitivity analyses and probability sensitivity analysis with 1,000 times of Monte Carlo simulations were conducted (see details of the statistical analysis of pharmacoeconomic analysis in Additional file).

Results

Baseline Characteristics

A total of 1,559 patients screened for eligibility, 700 were included (154 cases in the VAN/PTZ group, 158 cases in the VAN/CPZ-SBT group, 182 cases in the VAN/MEM group, 114 cases in the VAN/IPM-CIS group, and 92 cases in the other combination groups) (Fig. 1). Table 1 summarized the baseline characteristics of VAN/PTZ and VAN/BL groups. The matching was performed based on covariates with significant differences in the baseline characteristics between the two groups. The VAN/PTZ group and VAN/BL group were similar in age, gender, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, baseline Scr, and use of concomitant nephrotoxins. Patients receiving VAN/PTZ were more likely to have hypoproteinemia, malignancy and abdominal infections than patients receiving VAN/BL (all $P < 0.05$). We also performed subgroup analysis of the three combination therapies (VAN/CPZ-SBT, VAN/MEM, VAN/IPM-CIS) (Additional file Table S.2.).

Primary outcomes

In the matched cohort, the incidence of any AKI was higher among patients receiving VAN/PTZ compared to those receiving VAN/BL (Table 2). According to AKIN criteria, 43 patients in the VAN/PTZ group developed any AKI compared to 42 patients in the VAN/BL group (29.1% vs 12.5%, $P < 0.001$). Rates of stage 2 or 3 AKI was also higher based on AKIN criteria in the VAN/PTZ group than those of the VAN/BL group (18.2% vs 5.6%, $P < 0.001$). Moreover, rates of stage 2 or 3 AKI were higher in patients receiving VAN/PTZ than those receiving VAN/CPZ-SBT, VAN/MEM and VAN/IPM-CIS, respectively (Additional file Table S.3.).

Table 2
Outcomes Associated with Receipt of VAN/PTZ Compared to Receipt of Receiving VAN/other antipseudomonal β-lactams[1]

Variable	VAN/PTZ (n = 148)	VAN/other antipseudomonal β-lactams (n = 337)	*P* value
AKIN criteria			
AKI any stage	43 (29.1)	42 (12.5)	**< 0.001**
Stage 1	16 (10.8)	23 (6.8)	0.137
Stage 2	18 (12.2)	13 (3.8)	**0.001**
Stage 3	9 (6.1)	6 (1.8)	**0.025**
Stage 2 or 3	27 (18.2)	19 (5.6)	**< 0.001**
RIFLE criteria			
AKI any class	42 (28.4)	39 (11.6)	**< 0.001**
Risk	15 (10.1)	20 (5.9)	0.1
Injury	18 (12.2)	13 (3.8)	**0.001**
Failure	9 (6.1)	6 (1.8)	**0.025**
AKI per Vancomycin consensus guidelines	33 (22.3)	34 (10.1)	**< 0.001**
Duration of AKI	3.8 ± 3.8	3.3 ± 2.5	0.745
Return of renal function to baseline	2 (1.3)	1 (0.3)	0.981
Length of hospital [IQR]	22 (14–30)	23 (13–32)	0.970
Length of ICU stay [IQR]	18 (10–25)	20 (13–26)	**0.039**
Length of ICU stay-AKI subgroup	18 (9–23)	20 (13–25)	0.126

Statistically signifcant values are shown in bold.

VAN: Vancomycin; PTZ: Piperacillin-Tazobactam; AKI: Acute kidney injury; AKIN, Acute kidney injury network; RIFLE, risk, injury, failure, loss, end stage; IQR: Interquartile Range; RRT: Renal replacement therapy.

[1]: Other beta-lactams included meropenem (182/546, 33.4%), cefoperazone/sulbactam (158/546, 28.9%), imipenem/cisastatin (114/546, 20.9%), ceftriaxone (44/546, 8.1%), biapenem (27/546, 4.9%), ceftazidime (14/546, 2.6%), cefepime (4/546, 0.7%), latamoxef (3/546, 0.6%).

Variable	VAN/PTZ (n = 148)	VAN/other antipseudomonal β-lactams (n = 337)	*P* value
No. (%) with hospital mortality	11 (13.1)	29 (8.6)	0.657
No .(%) with hospital mortality-no. (%) in AKI subgroup	4 (2.7)	2 (0.6)	0.645
New RRT requirement	8 (5.4)	13 (3.8)	0.446
Microbiological response	98 (66.2)	226 (67.1)	0.814
Day of AKI occurrence	4.4 ± 1.7	4.1 ± 1.2	0.365
Statistically signifcant values are shown in bold.			
VAN: Vancomycin; PTZ: Piperacillin-Tazobactam; AKI: Acute kidney injury; AKIN, Acute kidney injury network; RIFLE, risk, injury, failure, loss, end stage; IQR: Interquartile Range; RRT: Renal replacement therapy.			
[1]: Other beta-lactams included meropenem (182/546, 33.4%), cefoperazone/sulbactam (158/546, 28.9%), imipenem/cisastatin (114/546, 20.9%), ceftriaxone (44/546, 8.1%), biapenem (27/546, 4.9%), ceftazidime (14/546, 2.6%), cefepime (4/546, 0.7%), latamoxef (3/546, 0.6%).			

Rates of any AKI were also higher in the VAN/PTZ group per RIFLE criteria (28.4% in the VAN/PTZ group vs 11.6% in the VAN/BL group, $P < 0.001$) and per vancomycin consensus guidelines (22.3% in the VAN/PTZ group vs 10.1% in the VAN/BL group, $P < 0.001$) (Table 2).

In addition, the Kaplan-Meier curve showed that the risk of any AKI in the VAN/PTZ group was significantly higher increased compared with the VAN/BL group based on AKIN criteria (Fig. 2).

Second outcomes

The intensive care unit (ICU) length of stay was significantly longer in the VAN/BL group than in the VAN/PTZ (20 vs 18 days, $P = 0.039$). Most patients in both groups (98.7% vs 99.7%) were unable to return to baseline renal function. There were no significant differences between the two groups in in-hospital mortality, the need for RRT, microbiological response, and day of AKI occurrence (Table 2).

Risk factors analysis for AKI

A total of 85 (17.5%) patients developed any AKI, and 46 (9.5%) patients developed stage 2 or 3 AKI. In multivariate regression analysis, the following variables were independent predictors of any AKI: VAN/PTZ (OR = 2.785, 95% CI = 1.659–4.669, $P < 0.001$), baseline eGFR ≤ 90 mL/min/1.73m^2 (OR = 2.089, 95% CI = 1.106–3.945, $P = 0.023$) (Additional file Table S.4.).

Moreover, in the multivariate analysis of subgroup, VAN/MEM, VAN/CPZ-SBT and VAN/IPM-CIS compared to VAN/PTZ, the risks of AKI in stage 2 or 3 were reduced by 78.8%, 71.3%, and 70.8%, respectively (Additional file Table S.5.).

Pharmacoeconomics analysis

The combinations of VAN/CPZ-SBT, VAN/MEM, and VAN/IPM-CIS were included in the decision tree model to compare with VAN/PTZ. The total costs and outcomes for the four treatment strategies are shown in Additional file Table S.6. In the empiric setting, ICERs per additional nephrotoxic episode of 1147.35$, 1845.11$, and 3989.95$ were found for VAN/PTZ relative to VAN/IPM-CIS, VAN/MEM, and VAN/CPZ-SBT, respectively (Table 3).

Table 3
Cost-effectiveness analysis for empiric therapy with vancomycin and β-lactams.

Combination Strategy	Total cost (USD)	Incremental cost (USD)	Effectiveness	Incremental effectiveness	ICER/nephrotoxic episode prevented (USD/rate of nephrotoxic episode prevented)
VAN/PTZ	2891.84		0.687		
VAN/IPM-CIS	2714.00	-177.84	0.842	0.155	-1147.35
VAN/MER	2465.62	-426.22	0.918	0.231	-1845.11
VAN/CPZ-SBT	2129.76	-762.08	0.878	0.191	-3989.95

VAN: Vancomycin; PTZ: Piperacillin-Tazobactam; CPZ-SBT: Cefperazone-Sulbactam; MEM: Meropenem; IPM-CIS: Imipenem-Cilastatin; ICER, ICER, incremental cost effectiveness ratio; USD, US dollar.

The results of one-way sensitivity analyses are shown in Additional file Figure S.4. For ICERs of VAN/CPZ-SBT or VAN/MEM vs VAN/PTZ, the cost of nephrotoxicity treatment had the greatest impact on the ICERs. However, the variation of this parameter had no substantial effect on the ICERs. For ICERs of VAN/IPM-CIS vs VAN/PTZ, OR of AKI for VAN/IPM-CIS vs VAN/PTZ had the greatest impact on the ICER. When the OR was set

as 0.64 (the AKI of VAN/IPM-CIS was 22.6%), ICER > 0. Monte Carlo simulation results revealed that the probabilities of VAN/CPZ-SBT, VAN/MEM, and VAN/IPM-CIS lower than VAN/PTZ were 100%, 99.8%, and 99.8%, respectively in the treatment costs.

Discussion

Current guidelines select empirical broad-spectrum treatments as the preferred strategy for sepsis patients, which led to the widespread use of antipseudomonal β-lactams and antibiotics for the treatment of resistant gram-positive bacteria infections (19). Recently, the incidence of AKI increased with VAN/PTZ treatment, which has raised concerns about the use of this combination therapy in the empiric setting. Our results showed that compared with VAN/BL, VAN/PTZ was significantly associated with increased risk of AKI in critically ill patients. Furthermore, pharmacoeconomics analysis showed that in empirical treatment, the ICERs per additional nephrotoxic episode of VAN/PTZ compared with VAN/IPM-CIS, VAN/MEM, and VAN/CPZ-SBT were 1147.35$, 1845.11$ and 3989.95$, respectively.

Our study had several strengths. First, our study excluded severe renal insufficiency patients (eGFR ≤ 30 mL/min/1.73m^2), which reduced the risk of bias in the results. The results of a previous study(8) may draw a vague conclusion since the study did not exclude severe renal insufficiency patients who are assumed to be at an increased risk of AKI. Second, critically ill patients have a high baseline risk of AKI due to the severity of diseases and comorbidities. In contrast to previous studies that had inadequately adjusted for AKI risk, we used propensity matching scores to control potential bias to compare differences in incidence of AKI between the two combination therapies. Third, previous studies evaluated any stage of AKI, assuming that all stages are equally deleterious (18, 20). In the current analysis, we focused on moderate to severe AKI, which is strongly associated with increased risk of morbidity and mortality (21). Fourth, VAN/PTZ may have a significant impact on kidney outcomes, resulting in increased mortality, hospital length of stay, and medical cost (22). Therefore, we performed a pharmacoeconomic analysis to further clarify the clinical applicability of combination therapy.

Although the AKI of VAN/PTZ is frequently reversible, short-term AKI may increase mortality for critically ill patients (23). Given reducing the frequency and the duration of VAN/PTZ may not always be possible to improve efficacy in clinical practice, clinicians may consider alternative combination therapies other than VAN/PTZ, such as VAN/CPZ-SBT, VAN/MEM, VAN/IPM-CIS, etc. to avoid the risk of AKI caused by VAN/PTZ. Meanwhile, the duration of VAN/PTZ could be limited to reduce the incidence of AKI (24). Currently, studies have proved that selecting alternative combination therapy or limiting the combined duration of VAN/PTZ could effectively reduce the incidence of AKI (25). The higher risk of stage 2 or 3 AKI in the VAN/PTZ group emphasizes the need for individualized treatment in the selection of an appropriate antibiotic. The rational use of antibiotics can not only effectively prevent bacterial resistance, but also improve the clinical outcomes of patients. The latter includes prevention the adverse events, such as AKI, which may have a certain impact on the kidney outcomes of patients. In particular, stage 2 or 3 AKI are associated with CKD progression, prolonged hospital stay and increased mortality (26). In addition, our study indicated that all combination treatments were at least 48–72 hours and AKI occurred within 7 days. In clinical practice, rapid diagnosis might help to early discontinue VAN/PTZ, thereby preventing the incidence of AKI.

PTZ monotherapy does not cause kidney injury in a prospective study (27). If the use of VAN/PTZ dose increase AKI risk, whereas, the mechanism of nephrotoxicity induced by VAN/PTZ remains unclear. People have hypothesized that subclinical interstitial nephritis caused by PTZ that is exacerbated by oxidative stress (reactive oxygen species production) may induce kidney injury (28). Neveretheless, interstitial nephritis is usually a rare event. It seems unlikely that a large increase of 9% AKI (defined by Scr) would occur since VAN/PTZ increases AKI risk through the mechanism of interstitial nephritis (10). Another hypothesis is that PTZ may reduce vancomycin clearance, resulting in the accumulation of vancomycin in the nephron (29). However, there is no mechanistic evidence to support these two hypotheses.

This study has several limitations. First, this study was a retrospective analysis, unpredictable factors may influnce the results. We fitted several multivariate models to adjust for factors to avoid the influence of other AKI risk factors on the results. Second, our study used Scr to determine the degree of kidney injury. However, Scr is not a direct indicator of kidney injury, rather it is a surrogate of glomerular function. More specific and sensitive biomarkers (such as kidney injury molecule-1 [KIM-1], osteopontin, etc.) are needed to determine whether they are associated with higher AKI when combination of VAN/PTZ. Third, we fail to assess the correlation between vancomycin trough concentration and the incidence of AKI in combination therapy due to lack of concentration data. Some researchers have found that there was no significant difference in the proportion of patients with vancomycin trough concentration > 15 mg/L or > 20 mg/L in the vancomycin/cefepime and the VAN/PTZ groups (30). Fourth, we fail to consider time-varying confounding. In critically ill patients, the risk of AKI potentially changes daily because exposures associated with AKI may change daily (e.g. nephrotoxins, blood pressure, organ function). The potential for AKI risk to change after ICU admission is not addressed.

Future studies evaluating AKI associated with combination therapy should consider stratification by baseline renal function in order to further explore the characteristics of this combination therapy. In addition, optimal strategies for managing VAN/PTZ-associated AKI should be determined for renal insufficiency patients, which could provide the possibility of preventing the incidence of AKI. Clinicians should recognize the risk factors of drug-induced AKI and closely monitor clinical response of patients during the course of treatment. Moreover, the mechanism of nephrotoxicity caused by VAN/PTZ has not been well characterized. Investigating the mechanism of nephrotoxicity has great significance to prevent the risk of nephrotoxicity and improve the clinical outcome of patients.

Conclusion

VAN/PTZ was associated with significantly higher incidence of AKI compared to VAN/BL in critically ill patients. In addition, patients receiving VAN/PTZ compared to VAN/CPZ-SBT, VAN/MEM, VAN/IPM-CIS could increase treatment cost when considering AKI occurrence. For critically ill patients who require empirical use of vancomycin and an antipseudomonal drug for antimicrobial therapy, clinicians should take a full consideration for institutional antimicrobial resistance patterns, possible pathogens, and the risk of AKI. Alternative combination therapies other than VAN/PTZ should also be considered. Further research is needed to illuminate the mechanism of AKI caused by VAN/PTZ.

Declarations

Ethics approval and consent to participate

This study was approved by all medical centers with a waiver of informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Concept and design: YZ, YW, YLD. Acquisition, analysis or interpretation of data: YZ, YW, JPL, RXY, LHY, YW, JHY, FS, KHZ, LRP, JLH, DL, XLJ, LHH, KKY, XEL, HFZ. Drafting of the manuscript: YZ, YW, YLS, BS, WLH, XTL, JPZ, YC, XNH, WWD, JZ, KJ, LZ, MCC, YSK. Critical revision of the manuscript for important intellectual content: all authors. All authors read and approved the final manuscript.

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Figures

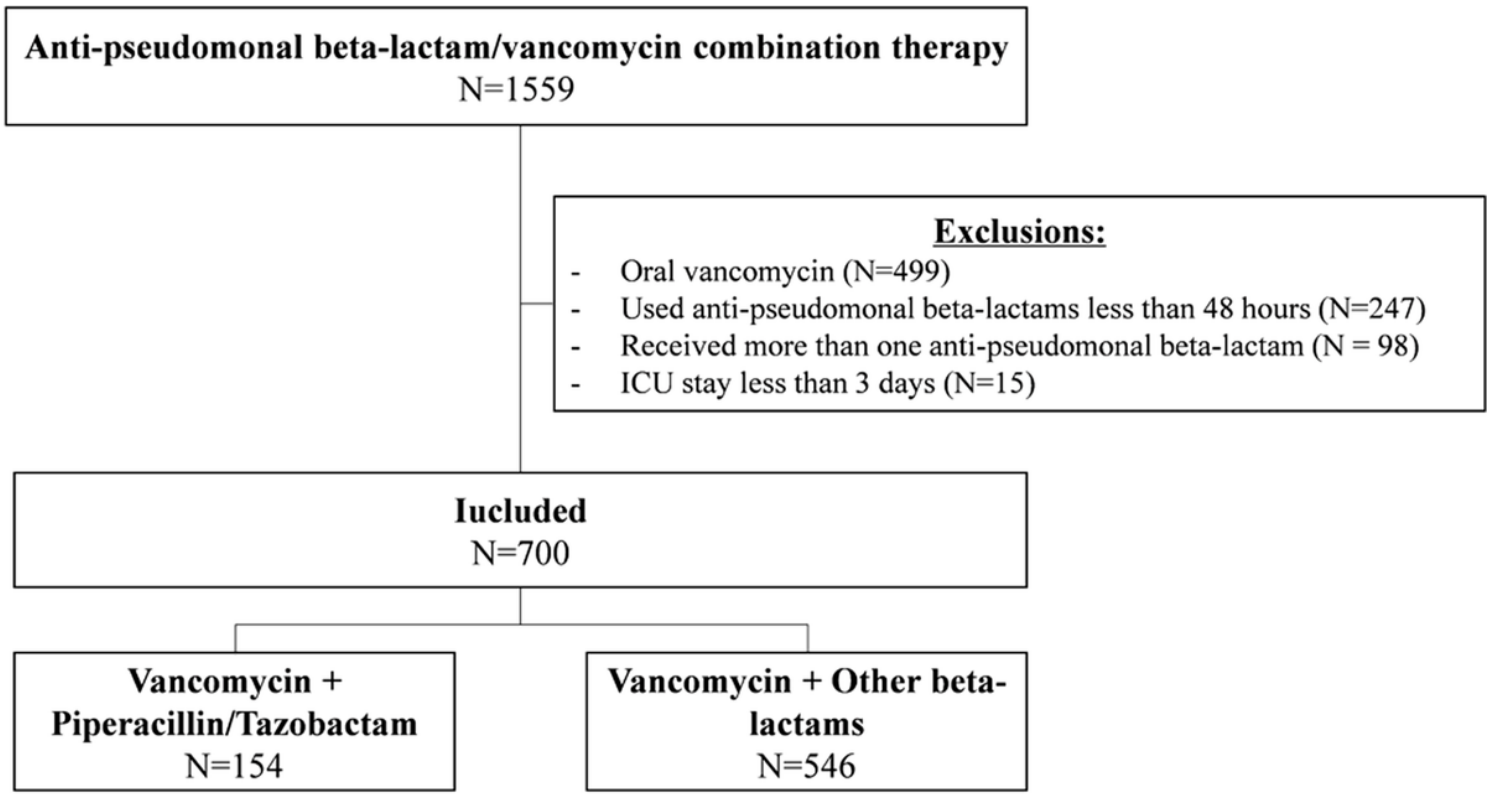

Figure 1

Study design and patient inclusion.

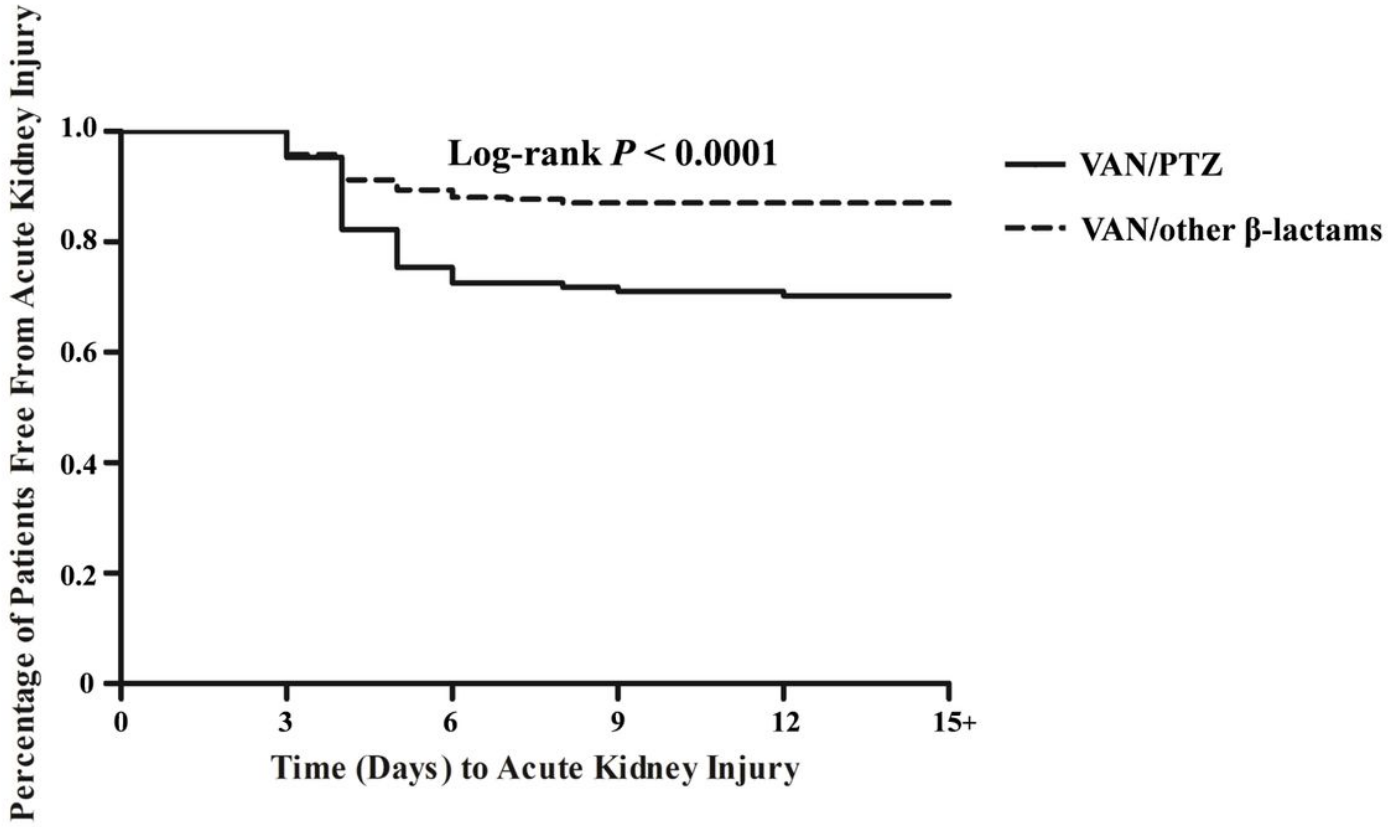

Figure 2

Kaplan-Meier curve for acute kidney injury based on AKIN criteria. VAN: vancomycin; VAN/PTZ: vancomycin/piperacillin-tazobactam.

Supplementary Files

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