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ORIGINAL ARTICLE

Vancomycin-induced acute kidney injury in elderly Chinese patients: a single-centre cross-sectional study

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Keywords acute kidney injury, older patients, risk factors, vancomycin

AIMS

The objective of the present study was to investigate the current situation concerning, and risk factors for, vancomycin (VAN)-induced acute kidney injury (VI-AKI) in elderly Chinese patients, to assess outcomes and risk factors in patients who have developed VI-AKI, in order to provide suggestions for improving the prevention and treatment of this condition in these patients.

METHOD

We retrospectively identified elderly older inpatients who had received four or more doses of VAN treatment. We compared patients with VI-AKI with those who received VAN treatment and had not developed AKI (NO-AKI). We defined VI-AKI as developing AKI during VAN therapy or within 3 days after withdrawal of VAN.

RESULTS

A total of 647 out of 862 elderly inpatients were included in the study. Among those excluded, in 89.3% of cases (192/215) this was because of lack of data on serum creatinine (SCr). Among included patients, 32.5% (210/647) of patients received therapeutic drug monitoring (TDM) during VAN therapy. In 66.9% of cases (424/634), there was insufficient TDM, and in 3.9% (25/634) this was appropriate. A total of 102 patients had confirmed VI-AKI, with an incidence of 15.8% (102/647). Multiple logistic regression analysis revealed that hyperuricaemia [odds ratio (OR) = 3.045; $P = 0.000$)], mechanical ventilation (OR = 1.906; $P = 0.022$) and concomitant vasopressor therapy (OR = 1.919; $P = 0.027$) were independent risk factors for VI-AKI; higher serum albumin (OR = 0.885; $P = 0.000$) was determined to be an independent protective factor for VI-AKI.

CONCLUSIONS

For the elderly Chinese patients treated with VAN, there was insufficient monitoring of SCr, too little use of VAN TDM, and lower rate of patients whose VAN though serum concentrations were not obtained at the correct time. We recommend that hospital managers increase investment in clinical pharmacists, to strengthen professional management. Patients with concomitant hyperuricaemia and on mechanical ventilation and vasopressor therapy should be paid more attention, and a higher serum albumin was determined to be an independent protective factor for VI-AKI.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Acute kidney injury (AKI) is the main serious adverse drug reaction associated with vancomycin (VAN) treatment and can lead to renal insufficiency or even death.
- A large number of studies have shown that older people, especially the elderly, due to their specific physiological status, are at higher risk for nephrotoxicity, and race may be a risk factor for VAN nephrotoxicity.
- However, the current data for VAN-induced (VI) AKI in elderly Chinese patients are very limit.

WHAT THIS STUDY ADDS

- For the elderly Chinese patients treated with VAN, there was insufficient monitoring of serum creatinine, too little use of VAN TDM, and lower rate of patients whose VAN though serum concentrations were obtained at the correct time.
- 102 patients had confirmed VI-AKI, with an incidence of 15.8% (102/647). Multiple logistic regression analysis revealed that concomitant hyperuricaemia, use of mechanical ventilation and concomitant vasopressor therapy were independent risk factors for VI-AKI; in addition, higher serum albumin was determined to be an independent protective factor for VI-AKI.
- We recommend that hospital managers increase investment in clinical pharmacists, to strengthen professional management. Patients with concomitant hyperuricaemia and on mechanical ventilation and vasopressor therapy should be paid more attention, and a higher serum albumin was determined to be an independent protective factor for VI-AKI.

Introduction

Vancomycin (VAN) is the important drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. To prevent resistance and ensure clinical efficacy, the clinical guidelines recommend always keeping trough levels above 10 mg l^{-1}, and a trough level of 15–20 mg l^{-1} is recommended in more serious infections [2]. However, acute kidney injury (AKI) is still the main serious adverse drug reaction (ADR) experienced by patients receiving VAN treatment, especially in septic patients admitted to the intensive care unit (ICU). The concomitance of other factors and the use of VAN makes it difficult to establish whether or not AKI is caused by VAN-induced nephrotoxicity. Thus, some authors have questioned whether high serum levels of VAN are the cause or a consequence of AKI [3–5]. Many factors are known to affect AKI development, although findings have not been consistent among studies [5]. The research of Bosso *et al*. showed that black race was a risk factor for VAN-induced nephrotoxicity (VIN) [6]. A large number of studies have shown that older people, especially the elderly, due to their specific physiological status, are at higher risk for nephrotoxicity [4, 7, 8]. With the increasing ageing of Chinese society, VAN-induced AKI (VI-AKI) in the elderly deserves more attention [9]. However, there have been few studies in elderly Chinese patients, and little is known about the risk factors for VI-AKI among Chinese individuals. A recent national survey on AKI in China revealed a serious issue with drug safety in the AKI population, as up to 70% of AKI patients had been exposed to potentially nephrotoxic drugs before or during their kidney injury, which is much higher than in developed countries (20–50%) [10]. The use of concomitant drugs has an important influence on VI-AKI. The individual agents that have been studied most extensively are aminoglycosides and piperacillin–tazobactam, but research on other potential toxins, such as Chinese patent medicines, is still needed [4]. The combination of multiple illnesses and use of complicated medications in elderly patients may make the issue of VI-AKI more serious. Meanwhile, data on of the outcome of elderly patients who have developed VI-AKI and on their risk factors are also limited, and deserving of further study. The objective of the present study was to assess the outcomes and identify the risk factors associated with VI-AKI in elderly Chinese patients, in order to provide suggestions for improving prevention and treatment in this population.

Methods

Study design and population

This was a single-centre retrospective study performed at ZhongShan Hospital, FuDan University. We recruited all elderly inpatients treated with VAN at our hospital from January 2016 to June 2017. The study was retrospective, and data were collected from the medical records of discharged patients. We did not need to obtain written informed consent from the patients whose records were used, as the study had received a Retrospective Clinical Application from ZhongShan Hospital. The study had received a Retrospective Clinical Application from ZhongShan Hospital. Patient data were anonymized prior to analysis. Another pharmacist, who was not participating in the study, was responsible for anonymizing these data.

The VI-AKI survey was designed to include three steps (see Figure 1). First, we screened the patients treated with VAN at our hospital; the inclusion criteria were: (i) ≥65 years of age; (ii) receiving four or more doses of VAN during treatment period. Patients were excluded if: (i) there was incomplete case information; (ii) they had received a kidney transplant; (iii) they had stage 5 chronic kidney disease (CKD) or were receiving regular dialysis; (iv) there were no serum creatinine (SCr) measurements available.

Secondly, we recorded the SCr of the included patients and separated the latter into two groups: those who had not developed AKI (NO-AKI) and the VI-AKI group. The definition of VI-AKI is the development of AKI during VAN therapy or within 3 days after the withdrawal of VAN. We used the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI as the major screening criterion [11]: an increase in SCr by ≥0.3 mg dl^{-1} (≥26.5 μmol l^{-1}) within 48 h or an increase in SCr to ≥1.5 times baseline which is known or presumed to have occurred within the prior 7 days.

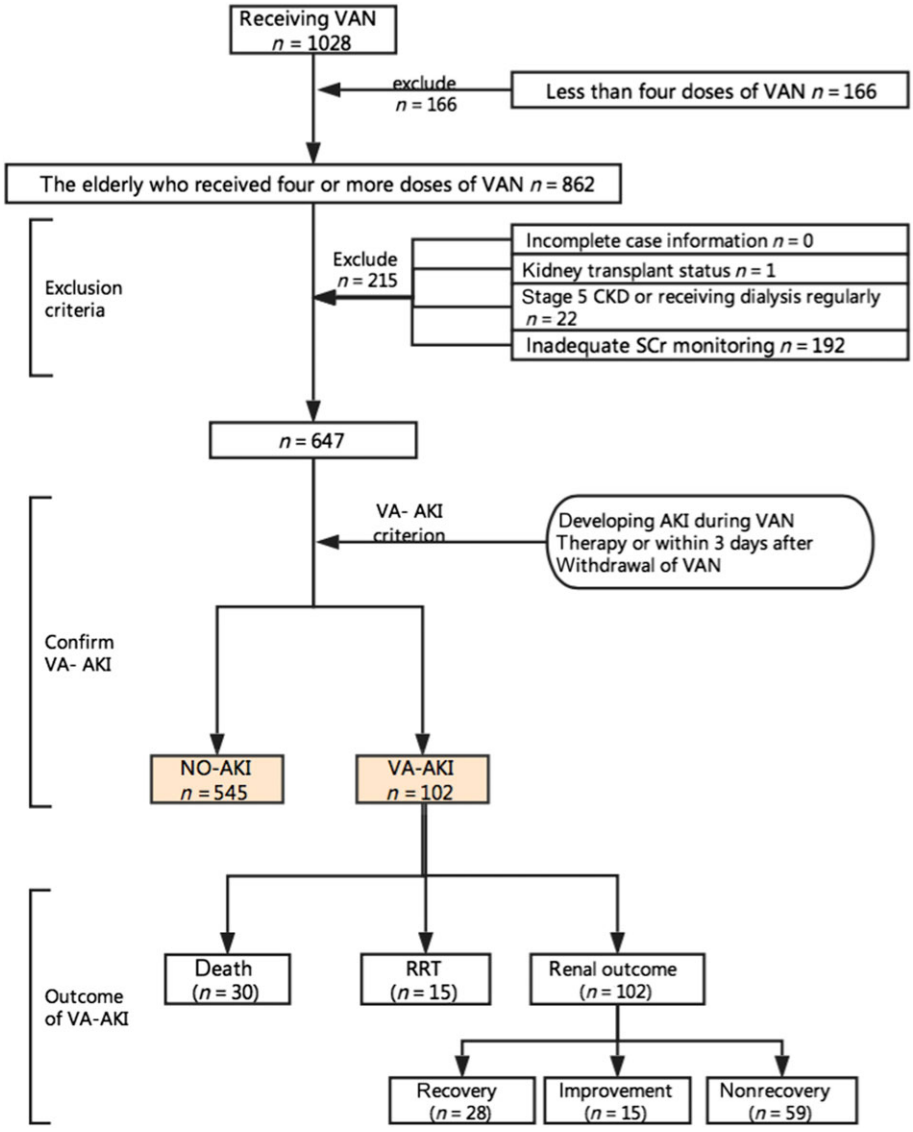

Figure 1

Study design. AKI, acute kidney injury; CKD, chronic kidney disease; NO-AKI, no development of AKI; RRT, renal replacement therapy; SCr, serum creatinine; VI-AKI, vancomycin-induced acute kidney injury; VAN, vancomycin

Thirdly, for the patients who developed AKI, we further analysed the development, severity and outcome of this condition. AKI severity was classified by the highest stage of AKI (1, 2, or 3) observed in the patient, according to the KDIGO criteria [11]. AKI outcome was examined using three variables: all-cause in-hospital death, receipt of renal replacement therapy (RRT) and renal outcome at discharge. Renal outcome was categorized into three levels: recovery, improvement and nonrecovery. Recovery was defined as restoration of the SCr level to baseline during hospitalization; improvement was defined as a decrease of at least 25% in the SCr level during hospitalization from the beginning of AKI onset; and nonrecovery was defined as a lack of improvement in the SCr level at discharge. We combined the recovery and improvement groups into one group for examination of the risk factors related to the renal outcome of VI-AKI.

Data collection

We collected data on the following variables: demographic characteristics (gender, age, weight), payment methods (basic national medical insurance, self-financing), inpatient department (medical, surgical, ICU), concomitant diseases [hypertension, diabetes, coronary heart disease (CHD), CKD and chronic lung disease (CLD), and chronic obstructive pulmonary disease (COPD)], laboratory variables [baseline estimated glomerular filtration rate (eGFR), serum albumin valley, presence or not of hyperuricaemia, peak serum lactic acid level), hospitalization-related factors [length of stay (LOS); ICU admittance; the presence or not of cancer, sepsis, hypotension and shock; the sequential organ failure assessment (SOFA); whether the patient had undergone surgery, whether the patient was on mechanical ventilation; whether death occurred]. The following variables concerning VAN

therapy and the use of concomitant drugs were also collected as comprehensively as possible: indication for VAN therapy (prophylactic, local infection, bacteraemia); variety of VAN (Wen kexin, Lai kexin); length of therapy (LOT); therapeutic drug monitoring (TDM); VAN dose adjustment; daily dose (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5 g); use of vasoactive drugs (nitrates, vasopressors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, dihydropyridines); and use of **doxazosin**, **hydrochlorothiazide**, **spironolactone**, **furosemide**, mannitol, **clopidogrel**, statins, sulphonylurea, **repaglinide**, antibiotics (piperacillin–tazobactam, cephalosporin, carbapenems, aminoglycosides, quinolones, macrolides, compound sulfamethoxazole, metronidazole/ornidazole), azole antifungal agents, **aciclovir**, contrast medium, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, calcineurin inhibitors, **mycophenolate mofetil**, **cyclophosphamide**, polyene phosphatidylcholine, edaravone, glutathione, acetylcysteine, phosphocreatine, levocarnitine, Chinese patent medicines (the root of red-rooted salvia, liquorice, kanglaite injection, xingnaojing injection).

Data analysis

Normally distributed continuous variables were expressed as the mean ± standard deviation (SD), and groups were compared using the independent Student's *t*-test. Non-normally distributed continuous variables were presented as the median [interquartile range (IQR)], and groups were compared using the rank-sum test. In addition, categorical variables were expressed as numbers (percentages) and analysed using the chi-squared test or Fisher's exact test. Further, logistic regression models were used to assess independent risk factors for VI-AKI incidence and outcome, and death. Multiple logistic regression models were used to identify variables with a *P* value of less than 0.2 in descriptive analysis; these variables were further examined in multivariate analysis to identify independent risk factors. The covariates included in multiple logistic regression analysis of VI-AKI incidence included: age (years); baseline SCr (mg dl^{-1}); serum albumin valley (g l^{-1}); hyperuricaemia (yes or no); LOS (days); ICU admittance (yes or no); SOFA (yes or no); shock (yes or no), mechanical ventilation (yes or no); variety of VAN (Wen kexin or Lai kexin); TDM (yes or no); VAN dose adjustment (yes or no); and use of nitrates (yes or no), vasopressors (yes or no), β-blockers (yes or no), spironolactone (yes or no), furosemide (yes or no), carbapenems (yes or no), compound sulfamethoxazole (yes or no), metronidazole/ornidazole (yes or no), azole antifungal agents (yes or no), steroids (yes or no), glutathione (yes or no), acetylcysteine (yes or no) and phosphocreatine(yes or no). A forward logistic model was used for the selection of variables. We used the same method to assess the independent risk factors for death and VI-AKI outcome. All *P* values were two-sided, and a *P* value of less than 0.05 was deemed significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 23.0 (IBM, 187 Chicago, IL, USA).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [12].

Results

Patients excluded and included

Of the 862 elderly inpatients who received four or more doses of VAN during treatment period, 647 were included in the study. The most common reason for patient exclusion was inadequate SCr monitoring to detect AKI development (89.3%; 192/215) (see Figure 2). Of the 647 patients included, 62.1% (402/647) were male, the median age was 71 years (IQR = 10) and 50.5% (327/647) were covered by basic national medical insurance. In addition, 31.2% (202/647) of patients also had hypertension, and the proportions of those with concomitant diabetes, CHD, CKD, CLD and COPD were 16.5% (107/647), 14.4% (93/647), 2.6% (17/647), 5.7% (37/647) and 5.4% (35/647), respectively. The average LOS was 24.1 (SD 25.9) days (see Table 1).

The VAN used in our hospital was obtained from two sources: Wen kexin [trade name: Wen kexin; generic name:

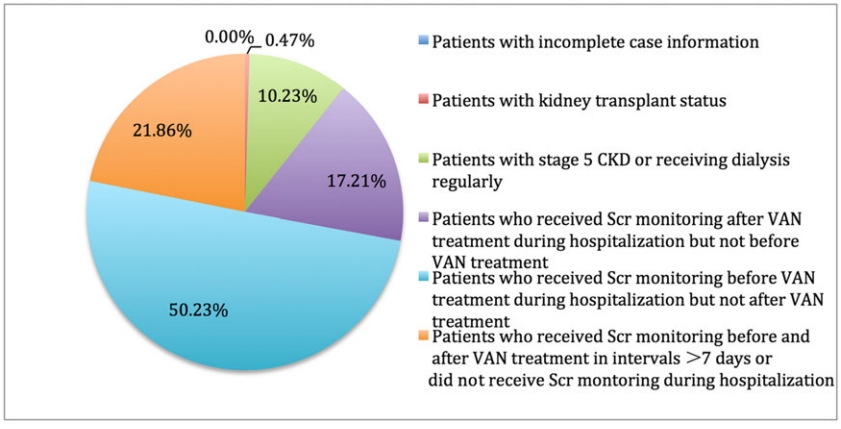

Figure 2

Frequency distribution of excluded patients. CKD, chronic kidney disease; SCr, serum creatinine; VAN, vancomycin

Table 1

Comparison of clinical characteristics between patients with vancomycin-induced acute kidney injury (VI-AKI) and those without (NO-AKI)

	Total (647)	NO-AKI (545)	VI-AKI (102)	*P*
Demographic factors:				
Male, *n* (%)	402 (62.1)	343 (62.9)	59 (57.8)	0.330
Age, median (IQR)	71 (10)	71 (9)	72 (10)	0.198
Payment methods:				0.443
Basic national medical insurance, *n* (%)	327 (50.5)	279 (47.1)	48 (51.2)	
Self-paying, *n* (%)	320 (49.5)	266 (48.8)	54 (52.9)	
In-patient department:				0.875
Medical *n* (%)	241 (37.4)	204 (36.3)	37 (37.6)	
Surgical *n* (%)	378 (58.6)	318 (58.6)	60 (58.8)	
ICU, *n* (%)	26 (4.0)	21 (4.9)	5 (3.9)	
Concomitant diseases:				
Hypertension, *n* (%)	202 (31.2)	165 (30.3)	37 (36.3)	0.23
Diabetes, *n* (%)	107 (16.5)	87 (16.0)	20 (19.6)	0.363
CHD, *n* (%)	93 (14.4)	78 (14.3)	15 (14.7)	0.917
CKD, *n* (%)	17 (2.6)	15 (2.8)	2 (0.3)	0.646
CLD, *n* (%)	37 (5.7)	30 (5.5)	7 (6.9)	0.588
COPD, *n* (%)	35 (5.4)	29 (5.3)	6 (5.9)	0.818
Laboratory variables:				
Baseline SCr, mg dl^{-1}	71.0 (34.0)	70.0 (33.0)	82.5 (59.5)	0.001
Baseline eGFR, ml min^{-1} 1.73 m^{-2}	97.8 ± 56.5	99.9 ± 57.2	83.0 ± 58.1	0.000
Serum albumin, g l^{-1}	28.7 ± 4.88	29.3 ± 4.79	26.6 ± 4.87	0.000
Hyperuricaemia, *n* (%)	304 (47.0)	229 (42.0)	75 (73.5)	0.000
Peak serum lactic acid, mmol l^{-1}	3.20 (4.43)	3.05 (3.30)	3.30 (5.00)	0.403
Hospitalization-related factors:				
LOS (days), median (IQR)	24.1 (25.9)	23.3(24.5)	27.1 (28.4)	0.064
ICU admittance, *n* (%)	178 (27.5)	143 (26.2)	35 (34.3)	0.094
Cancer, *n* (%)	151 (23.3)	127 (23.3)	24 (23.5)	0.96
Sepsis *n* (%)	34 (5.3)	23 (4.2)	11 (10.8)	0.006
Hypotension, *n* (%)	28 (4.3)	20 (3.7)	8 (7.8)	0.102[a]
SOFA, *n* (%)	40 (6.2)	27 (5.0)	13 (12.7)	0.003
Shock, *n* (%)	75 (11.6)	51 (9.4)	24 (23.5)	0.000
Surgery, *n* (%)	386 (59.7)	324 (59.4)	62 (60.8)	0.801
Mechanical ventilation, *n* (%)	405 (62.6)	325 (59.6)	80 (78.4)	0.000
Death, *n* (%)	95 (14.7)	65 (11.9)	30 (29.4)	0.000

CHD, coronary heart disease; CKD, chronic kidney disease; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LOS, length of stay; SOFA, sequential organ failure assessment; SCr, serum creatinine

[a]Continuity correction

vancomycin hydrochloride for injection; manufacturer: Vianex Sa (Plantc), Athens, Greece; specification: 500 mg bottle^{-1}; 66.0% (427/647) of patients were treated with VAN from this source) and Lai kexin (trade name: Lai kexin; generic name: vancomycin hydrochloride for injection; manufacturers: Zhejiang Medicine Co., Ltd and Xinchang Pharmaceutical Factory, XinChang City, ZheJiang Province, China; specification: 500 mg bottle^{-1}). The reasons for VAN treatment were mainly local infection and bacteraemia, corresponding to 69.9% (452/647) and 25.0% (162/647), respectively. The median LOT was 5.6 days (IQR = 6.2), and the most frequently used daily doses were 1.0 g, 1.5 g and 2.0 g, with 27.6% (178/647), 26.0% (168/647) and 38.7% (250/647) of patients, respectively using these doses. We also analysed 41 types of drugs used concomitantly by the patients receiving VAN treatment (see Table 2).

TDM of included patients

A total of 32.5% (210/647) of the patients received TDM during VAN therapy. The judgement as to whether a patient required TDM was based on a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists [13] and a consensus of Chinese experts [14]; 634 patients met the requirements of the former, and all patients met the requirements of the latter. The proportion of patients in whom TDM was inadequate was 66.9% (424/634) for the American consensus and 67.5% (437/647) for the Chinese consensus. We further analysed the time of trough samples obtained for TDM and found that this was appropriate in 3.9% of cases (25/634) for the American consensus, and 8.2% (53/647) for the Chinese consensus (see Table 3).

Clinical characteristics of VI-AKI

A total of 102 patients developed VI-AKI, corresponding to an incidence of 15.8% (102/647); 57.8% (59/102) of these were male and the median age was 72 years (IQR = 10). There was no significance difference between patients with and without VI-AKI in terms of their concomitant diseases, including hypertension, diabetes, CHD, CKD, CLD and COPD. In terms of laboratory variables, patients with VI-AKI were more likely than those without to have a lower baseline eGFR (99.9 ± 57.2 *vs*. 83.0 ±58.1; P = 0.000), a lower serum albumin valley (29.3 ± 4.79 *vs*. 26.6 ± 4.87; P = 0.000) and hyperuricaemia (42.0% *vs*. 73.5%; P = 0.000). We also analysed hospitalization-related factors. No significance difference was found between the groups in LOS, ICU admittance, the presence or not of cancer and whether or not they had undergone surgery. VI-AKI patients were more likely have had sepsis (4.2% *vs*. 10.8%; P = 0.006), to have undergone a SOFA (5.0% *vs*. 12.7%; P = 0.003), to have gone into shock (9.4% *vs*. 23.5%) and to have received mechanical ventilation (59.6% *vs*. 78.4%; P = 0.000) (see Table 1). When we further analysed the cause of shock, the main cause was septic shock, with an incidence of 60% (45/75) (see Table S1).

Concomitant drugs taken by those with VI-AKI

We further analysed 41 types of drug taken by patients while receiving VAN treatment. Patients with VI-AKI were significantly more likely than those without to be taking a vasopressor (12.1% *vs*. 29.4%; P = 0.000). Among the diuretics (hydrochlorothiazide, spironolactone, furosemide), only furosemide use was found to be significantly higher in VI-AKI patients (60.9% *vs*. 77.5%; P = 0.001) than in others. Compared with the NO-AKI patients, significantly more VI-AKI patients were taking carbapenems (78.9% *vs*. 93.1%; P = 0.001), compound sulfamethoxazole (3.7% *vs*. 10.8%; P = 0.002), azole antifungal agents (18.7% *vs*. 29.4%; P = 0.022) and steroids (25.3% *vs*. 38.2%; P = 0.007). VI-AKI patients were also more likely to be taking glutathione (45.7% *vs*. 58.8%; P = 0.015), acetylcysteine (25.7% *vs*. 36.3%; P = 0.028) and phosphocreatine (8.1% *vs*. 15.7%, P = 0.015). Chinese patent medicines (the root of red-rooted salvia, liquorice, kanglaite injection, xingnaojing injection) were analysed and no significantly differences were found in their use between patient groups (see Table 2).

Risk factors for VI-AKI

Multiple logistic regression analysis revealed that hyperuricaemia [odds ratio (OR) = 3.045; P = 0.000), mechanical ventilation (OR = 1.906; P = 0.022) and concomitant vasopressor therapy (OR = 1.919; P = 0.027) were independent risk factors for VI-AKI; serum albumin valley (OR = 0.885; P = 0.000) was determined to be an independent protective factor for VI-AKI. The goodness of fit was evaluated using the analysis of Hosmer and Lemeshow, and found to be 0.798 (see Table 4).

VI-AKI severity and treatment

VI-AKI severity was classified according to the highest stage of AKI observed in the patient. The highest disease stage was stage 1 for 61.8% (63/102) of the patients and 26.5% (27/102) were stage 3 (see Table S2). Therapy adjustments, including termination of VAN treatment or adjustment in the dose, took place in only 45.1% (46/102) of these VI-AKI patients after the onset of AKI, and 14.7% (15/102) received RRT (see Table 5).

Outcomes and risk factors for VI-AKI

The all-cause in-hospital mortality rate for VI-AKI patients was 29.4% (30/102). Multiple logistic regression analysis revealed that the independent risk factors for death were the presence of diabetes (OR = 11.178; P = 0.005), concomitant metronidazole/ornidazole (OR = 46.171; P = 0.001) and steroids (OR = 7.696; P = 0.005). Payment methods (OR = 0.026; P = 0.000) and high serum albumin levels (OR = 0.809; P = 0.011) were independent protective factors (see Table 6). We separated the renal outcomes of the VI-AKI patients into three categories: recovery, improvement and nonrecovery. Renal function recovered in 28 patients, with a median recovery time of 7.7 days (IQR = 14.8) after receipt of VAN therapy, and renal function improved in 15 patients, with a median recovery time of 4.0 days (IQR = 3.3). Thus, 43 patients showed either recovery or improvement, representing 42.2% (43/102) of the total VI-AKI patient group. The remaining 57.8% (59/102) of the VI-AKI patients had renal insufficiency at the time of hospital discharge. Multiple logistic regression analysis revealed that payment methods (OR = 5.353; P = 0.006), the presence of CHD (OR = 6.197; P = 0.041), and taking contrast medium (OR = 4.326; P = 0.016) were independent risk factors for renal

Table 2

Comparison of concomitant drugs used between patients with vancomycin-induced acute kidney injury (VI-AKI) and those without (NO-AKI)

	Total (*n* = 647)	NO-AKI (*n* = 545)	VI-AKI (*n* = 102)	*P*
Indication for VAN therapy, *n* (%) #1:				0.190
Prophylactic, *n* (%)	33 (5.1)	29 (5.3)	4 (3.9)	
Local infection, *n* (%)	452 (69.9)	373 (68.4)	79 (77.5)	
Bacteraemia, *n* (%)	162 (25)	143 (26.2)	19 (18.6)	
Variety of VAN:				0.015
Wen kexin, *n* (%)	427 (66.0)	349 (64.0)	78 (76.5)	
Lai kexin, *n* (%)	220 (34.0)	196 (36.0)	24 (23.5)	
LOT, median (IQR)	5.6 (6.2)	5.8 (6.0)	5.5 (7.5)	0.468
TDM, *n* (%)	210 (32.5)	161 (29.6)	49 (48.0)	0.000
Daily dose:				0.274
0.5 g, *n* (%)	45 (7.0)	32 (5.9)	13 (12.7)	
1.0 g, *n* (%)	178 (27.6)	151 (27.8)	27 (26.5)	
1.5 g, *n* (%)	168 (26.0)	142 (26.1)	26 (25.5)	
2.0 g, *n* (%)	250 (38.7)	215 (39.5)	35 (34.3)	
2.5 g, *n* (%)	1 (0.2)	1 (0.2)	0 (0)	
3.0 g, *n* (%)	1 (0.2)	1 (0.2)	0 (0)	
5.0 g, *n* (%)	3 (0.5)	2 (0.4)	1 (1.0)	
Concomitant drugs:				
Nitrate, *n* (%)	304 (47.0)	249 (45.7)	55 (53.9)	0.126
Vasopressor, *n* (%)	96 (14.8)	66 (12.1)	30 (29.4)	0.000
Doxazosin, *n* (%)	8 (1.2)	5 (0.9)	3 (2.9)	0.227[a]
ACEI, *n* (%)	84 (13.0)	67 (12.3)	17 (16.7)	0.228
ARB, *n* (%)	72 (11.1)	61 (11.2)	11 (10.8)	0.904
β-Blocker, *n* (%)	349 (53.9)	288 (52.8)	61 (59.8)	0.196
DHP, *n* (%)	183 (28.3)	154 (28.3)	29 (28.4)	0.971
Hydrochlorothiazide, *n* (%)	41 (6.3)	34 (6.2)	7 (6.9)	0.812
Spironolactone, *n* (%)	332 (51.3)	272 (49.9)	60 (58.8)	0.098
Furosemide, *n* (%)	411 (63.5)	332 (60.9)	79 (77.5)	0.001
Mannitol, *n* (%)	44 (6.8)	35 (6.4)	9 (8.8)	0.377
Clopidogrel, *n* (%)	96 (14.8)	85 (15.6)	11 (10.8)	0.210
Statin, *n* (%)	164 (25.3)	136 (25.0)	28 (27.5)	0.595
Sulphonylurea, *n* (%)	27 (4.2)	23 (4.2)	4 (3.9)	1.000[a]
Repaglinide, *n* (%)	9 (1.4)	8 (1.5)	1 (1.0)	1.000[b]
Piperacillin–tazobactam, *n* (%)	35 (5.4)	27 (5.0)	8 (7.8)	0.236
Cephalosporin, *n* (%)	536 (82.8)	449 (82.4)	87 (85.3)	0.474
First-generation cephalosporin, *n* (%)	105 (16.2)	91 (16.7)	14 (13.7)	0.445
Second-generation cephalosporin, *n* (%)	299 (46.2)	251 (46.1)	48 (47.1)	0.852
Third-generation cephalosporin, *n* (%)	323 (49.9)	267 (49.0)	56 (54.9)	0.273
Fourth-generation cephalosporin, *n* (%)	73 (11.3)	61 (11.2)	12 (11.8)	0.867
Carbapenem *n* (%)	525 (81.1)	430 (78.9)	95 (93.1)	0.001

(continues)

Table 2

(Continued)

	Total (*n* = 647)	NO-AKI (*n* = 545)	VI-AKI (*n* = 102)	*P*
Aminoglycoside, *n* (%)	48 (7.4)	40 (7.3)	8 (7.8)	0.859
Quinolone, *n* (%)	292 (45.1)	242 (44.4)	50 (49.0)	0.390
Macrolide, *n* (%)	27(4.2)	25(4.6)	2(2.0)	0.343[a]
Compound sulfamethoxazole, *n* (%)	31 (4.8)	20 (3.7)	11 (10.8)	0.002
Metronidazole/ornidazole, *n* (%)	91 (14.1)	71 (13.0)	20 (19.6)	0.079
Azole antifungal agent, *n* (%)	132 (20.4)	102 (18.7)	30 (29.4)	0.022
Acyclovir, *n* (%)	24 (3.7)	19 (3.5)	5 (4.9)	0.683[a]
Contrast medium, *n* (%)	222 (34.3)	190 (34.9)	32 (31.4)	0.496
NSAID, *n* (%)	238 (36.8)	197 (36.1)	41 (40.2)	0.436
Steroid, *n* (%)	177 (27.4)	138 (25.3)	39 (38.2)	0.007
Calcineurin inhibitor, *n* (%)	13 (2.0)	10 (1.8)	3 (23.1)	0.729[a]
Mycophenolate mofetil, *n* (%)	9 (1.4)	6 (1.1)	4 (2.9)	0.319[a]
Cyclophosphamide, *n* (%)	16 (2.5)	13 (2.4)	3 (2.9)	1.000[a]
Polyene phosphatidylcholine, *n* (%)	30 (4.6)	26 (4.8)	4 (3.9)	0.906[a]
Edaravone, *n* (%)	17 (2.6)	0 (0)	17 (3.1)	0.09[b]
Glutathione, *n* (%)	309 (47.8)	249 (45.7)	60 (58.8)	0.015
Acetylcysteine, *n* (%)	177 (27.4)	140 (25.7)	37 (36.3)	0.028
Phosphocreatine, *n* (%)	60 (9.3)	44 (8.1)	16 (15.7)	0.015
Levocarnitine, *n* (%)	48 ((7.4)	41 (7.5)	7 (6.9)	0.815
The root of red-rooted salvia, *n* (%)	27 (4.2)	21 (3.9)	6 (5.9)	0.502[a]
Liquorice, *n* (%)	102 (15.8)	68 (15.2)	34 (16.9)	0.590
Kanglaite injection, *n* (%)	23 (3.6)	20 (3.7)	3 (2.9)	0.941[a]
Xingnaojing injection, *n* (%)	46 (7.1)	38 (7.0)	8 (7.8)	0.917[a]

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, dihydropyridine; IQR, interquartile range; LOT, length of therapy; NSAID, nonsteroidal anti-inflammatory drug; TDM, therapeutic drug monitoring; VAN, vancomycin

[a]Continuity correction

[b]Fisher's exact test

Table 3

TDM situation according the American and Chinese consensuses

	P received TDM (*n*)	TDM rate (%)	P required TDM (*n*)	TDM R of reaching consensus (%)	Inadequate TDM R (%)	Correct TDM time (*n*)	R of correct TDM (%)
America	210	32.5	634	33.1	66.9	25	3.9
China	210	32.5	647	32.5	67.5	53	8.2

Correct TDM time: American consensus for TDM: Trough samples should be obtained just before the fourth dose in patients with normal renal function, to ensure that target concentrations are attained. TDM Chinese consensus: Trough samples should be obtained just before the third dose of VAN therapy or before the fourth dose of VAN therapy. P, patients; R, rate; TDM, therapeutic drug monitoring; VAN, vancomycin

Table 4

Risk factors for vancomycin-induced acute kidney injury

Factors	*P* value	OR	95% CI
Serum albumin	0.000	0.885	0.843, 0.928
Hyperuricaemia	0.000	3.045	1.834, 5.057
Mechanical ventilation	0.022	1.906	1.098, 3.310
Vasopressor	0.027	1.919	1.078, 3.418

CI, confidence interval; OR, odds ratio

Table 5

Treatment characteristics for vancomycin-induced acute kidney injury

Treatment	*N* (%)
No adjustment	41 (40.2)
Termination of VAN	24 (23.5)
Dose adjustment	22 (21.6)
RRT	15 (14.7)

RRT, renal replacement therapy; VAN, vancomycin

Table 6

Risk factors for death in patients with vancomycin-induced acute kidney injury

Factors	*P* value	OR	95% CI
Payment methods	0.000	0.026	0.003, 0.198
Diabetes	0.005	11.178	2.092, 59.720
Serum albumin	0.011	0.809	0.688, 0.953
Metronidazole/ornidazole	0.001	46.171	4.790, 445.052
Steroid	0.005	7.696	1.828, 32.396

CI, confidence interval; OR, odds ratio

outcome in VI-AKI patients (see Table 7). We performed an additional post-estimation analysis using the Akaike score (see Table 8).

Discussion

VAN is often associated with nephrotoxicity. Older age has been found to be significantly associated with nephrotoxicity in patients receiving VAN [4]. Elderly patients are more likely to have combination of multiple illnesses and take complicated medications, which may give rise to VI-AKI. This single-centre retrospective study conducted at our hospital aimed to investigate the current situation concerning

Table 7

Risk factors for renal outcome in patients with vancomycin-induced acute kidney injury

Factors	*P* value	OR	95% CI
Payment methods	0.006	5.353	1.623, 17.659
CHD	0.041	6.197	1.074, 35.749
Contrast medium	0.016	4.326	1.313, 14.248

CHD, coronary heart disease; CI, confidence interval; OR, odds ratio

Table 8

Akaike score

Goodness-of-fit evaluation	Risk factors for VI-AKI	Risk factors for death	Risk factors for renal outcome
Akaike score	518.977	84.142	120.508

VI-AKI, vancomycin-induced acute kidney injury

VI-AKI in elderly Chinese patients and identify its risk factors, to provide some suggestions for improving the prevention and treatment of AKI.

We conducted a three step-survey to identify the VI-AKI population. In the first step, 89.3% patients were excluded because of inadequate SCr monitoring, which highlighted the fact that clinicians may need to pay more attention to patients' renal function after receiving VAN treatment, and the possibility of a missed diagnosis of VI-AKI. The study by Van Hal *et al*. also demonstrated that clinicians should closely monitor the renal function of patients receiving VAN [15]. We then investigated the TDM situation of the patients included. According to the American consensus for TDM, the proportion of patients in whom TDM was inadequate was 66.9% (compared with 67.5% for the Chinese consensus). The main reasons for the relatively low TDM rate were that, firstly, TDM for VAN was first used in our hospital in November 2015; prior to this, patients receiving VAN did not undergo TDM. Clinicians adjust the VAN dose based on patients' therapeutic effect (such as body temperature, routine blood test results, bacterial cultures, etc.) and adverse reactions (such as the SCr value). As TDM for VAN had been in use for only 1.5 years, clinicians may have not have developed a familiarity with VAN TDM in accordance with the guidelines. In this regard, it is necessary for clinicians to develop an understanding of the importance of VAN concentration monitoring. Secondly, China's clinical pharmacy system is still in its initial and exploratory stage. Although our hospital is one of the most developed in this field in China, clinical pharmacists can still only cover key clinical departments, such as the departments of infectious diseases, respiratory medicine, cardiology, neurology and ICU, to optimize clinical drug use, and because of their work, the TDM rate is higher in these departments. However, in surgical departments, surgeons focus more on surgical rather drug therapy issues,

so the appropriate use of VAN and monitoring for adverse drug reactions would have been weaker. Both of the two reasons are likely to have contributed to the low TDM rate. The TDM correction was also a problem, only 3.9% patients' trough samples of VAN for TDM were obtained at the right time (compared with 8.2% for the Chinese consensus). The low proportion of cases in which TDM of VAN was carried out correctly was mainly the result of clinicians' lack awareness of the guidelines for the therapeutic monitoring of VAN, and clinical pharmacists' poor management of the appropriate use of this agent. Given the recommendations to increase serum VAN concentrations to 15–20 mg l^{-1} to combat rising minimal inhibitory concentrations (MICs), this information reinforces the valuable role that TDM plays in optimizing the safe use of VAN [16]. In addition, the serum VAN concentration is one of the most important bases for dose adjustment. However, Moffett *et al*. [17] and Otto *et al*. [18] found that, even with close monitoring of the serum concentration, levels above the upper limit of the target level could occur, which aggravated this problem. The results of TDM and dose adjustment should be analysed by clinical pharmacists for the results of TDM and dose adjustment is also very important. Panwar *et al*. [19] conducted a study in patients with CKD and suggested frequent drug level monitoring subsequently, to minimize VIN risk. In elderly patients, who have a certain degree of renal dysfunction, this calls for more attention. A meta-analysis showed that TDM not only decreased the rate of nephrotoxicity significantly, but also could increase clinical efficacy in patients treated with VAN [20]. Katikaneni *et al*. [21] found that regular monitoring (preferably twice weekly) of SCr and VAN trough levels was advisable for minimizing VAN-associated AKI. Smith *et al*. [22] conducted a pharmacist-initiated VAN monitoring programme and evaluated its effect. The overall incidence of AKI decreased from 16.3% to 4.7% (P = 0.013). Implementation of pharmacist-driven VAN monitoring significantly improved compliance with monitoring VAN serum levels and kidney function, and also reduced the incidence of AKI in the long-term care setting [22]. In our hospital, the main reasons for the low levels of TDM and lower rate of patients whose VAN though serum concentrations were obtained at the correct time were mainly because of clinicians' lack awareness of the guidelines for the therapeutic monitoring of VAN and clinical pharmacists' poor management of the appropriate use of this agent. Compared with clinicians, clinical pharmacists have a wealth of expertise in drug safety and appropriate use. We suggest that hospital managers increase the input of clinical pharmacists, not only to improve the management of VAN use, but also to free up more of clinicians' time to focus on their diagnosis of the disease. Physician–pharmacist collaboration is also cost-effective, as has been demonstrated in many other cases of disease management [23–26].

A major feature of elderly patients is the combined incidence of multiple diseases. In a further analysis comparing NO-AKI with VI-AKI patients, our study incorporated as many pathophysiological states as possible. There was no significance difference between patients with and without VI-AKI in terms of their concomitant diseases, but VI-AKI patients were more likely also to have had sepsis, to have undergone a SOFA, to have gone into shock and to have undergone surgery. More concomitant risk factors may have contributed to their higher risk of AKI development. Multivariate regression analysis showed that mechanical ventilation was an independent risk factor for VI-AKI. This was the first demonstration of mechanical ventilation use as an independent risk factor for VI-AKI in elderly Chinese patients. Liu *et al*. [8] previously showed that mechanical ventilation is a risk factor for AKI and has a statistically significant interaction with age. The explanation for this may be that mechanical ventilation use is one of the variables of illness severity.

Our study included several laboratory data on the factors reflecting the clinical conditions. VI-AKI patients were more likely to have a lower baseline eGFR, lower serum albumin valley and hyperuricaemia. Multivariate regression found that hyperuricaemia was an independent risk factor and that serum albumin valley was an independent protective factor. Hyperuricaemia has rarely been analysed in previous studies. Liu Y *et al*. [27] published a case report on acute renal failure induced by primary hyperuricaemia in children. In their review, Ejaz *et al*. [28] proposed that hyperuricaemia might contribute pathogenetically to renal vasoconstriction as well as to endothelial dysfunction, an inflammatory response, oxidative stress and the disturbances in autoregulation that occur with acute kidney failure, and affect renal outcomes adversely. In another study, these authors suggested that the measurement of serum uric acid levels offers the potential to predict AKI at any perioperative time point [29]. This was the first time that hyperuricaemia was demonstrated to be an independent factor for VI-AKI. These results should act as a reminder to clinicians to pay more attention to patients with hyperuricaemia when considering administering VAN to them. When giving VAN, an intervention on uric acid may be superior, but this needs to be established in further, well-designed studies. Our study also demonstrated that the serum albumin valley was an independent protective factor. The serum albumin valley in patients with VI-AKI was significantly lower than in those without (P = 0.000). It was first to demonstrate that a lower serum albumin valley is significantly associated with VI-AKI. In the study by Burgess *et al*. [30], hypoalbuminaemia was found to be one of the factors predisposing patients to drug-induced AKI. Wiedermann *et al*. [31], in a meta-analysis, also found that hypoalbuminaemia was a significant independent predictor of AKI, and that the renoprotective action of albumin was mediated by its ability to scavenge reactive oxygen species, preventing oxidative damage, and binding and delivering protective lysophosphatidic acid. It is advisable for clinicians to be aware of patients' serum albumin levels, to avoid hypoalbuminaemia, when giving VAN therapy.

The use of complicated medications is another feature of elderly patients. We included 41 different types of drug taken by patients alongside VAN treatment that may have had an effect on VI-AKI. Compared with the vast majority of studies, the classification of drugs was more detailed and the variety of drugs more comprehensive in our study, and we also included Chinese patent medicines. Even though diuretics present a risk factor for the development of VI-AKI, most studies have included only loop diuretics or diuretics [7, 32]. We specifically classified diuretics into hydrochlorothiazide, spironolactone or furosemide. Our study showed that furosemide was the only type of diuretic that was significantly more likely to be taken by VI-AKI patients concomitantly with

VAN. This was similar to the results of studies in younger adults [4]. The selection of diuretics in patients receiving VAN may be an important consideration. The effect of administering Chinese patent drugs concomitantly with VAN on the development of VI-AKI was demonstrated in a study in a Chinese adult population [33]. The present study was the first to explore the influence of Chinese patent drugs on VI-AKI in elderly Chinese patients being treated with VAN. Our study showed no significant difference between the groups taking and not taking Chinese patent drugs. This might have been because our study population took only small amounts of Chinese patent drugs. We also analysed the effect in this patient group of taking concomitant antioxidants. Many studies have suggested that oxidative stress is one of the main pathogenic mechanisms in VIN, and that the use of antioxidants decreases the severity of VIN [34]. In various experimental models, numerous antioxidants have been shown to be protective against VIN [4]. We included drugs with antioxidant activity (polyene phosphatidylcholine, edaravone, glutathione, acetylcysteine, phosphocreatine, levocarnitine). Of these, we found that VI-AKI patients were significantly more likely to be taking glutathione, acetylcysteine and phosphocreatine, which was not consistent with the results of previous studies. This may have been because of the complicated concomitant diseases and medications associated with elderly patients. The individual agents most extensively studied in the previous studies include aminoglycosides and piperacillin–tazobactam; both were independent risk factors and significantly associated with a higher level of occurrence of VI-AKI. However, we did not find any difference in the level of occurrence of VI-AKI between the groups taking and not taking these agents. This is likely to have been because elderly patients are at high risk of VI-AKI, and clinicians will avoid combined therapy if possible. Multivariate regression analysis showed that taking a vasopressor was an independent risk factor for VI-AKI, which was consistent with previous findings. Vasopressors are capable of affecting kidney function, and patients receiving these agents are more likely to be in a critically ill state [4, 16].

We further analysed the outcomes of elderly patients with VI-AKI, which has rarely been performed in previous studies. In our study, 61.8% of elderly patients with VI-AKI had stage 1 disease and 14.7% received RRT. A prospective observational study of AKI in an elderly population showed that the severity of the disease and the need for dialysis were significantly associated with mortality [35]. Once AKI has developed, there are few effective means of treating it. Dialysis is a final resort for treating AKI. Petronijevic *et al.* [36] conducted a study to measure the effect of treatment on short-term outcomes in elderly patients with AKI and found no significant difference in survival during the follow-up period up to 90 days between the haemodialysis- and conservatively treated group. Another study showed that high-dose and low-dose haemofiltration produce similar outcomes in AKI patients [37]. The most important factor in improving patient outcomes and reducing medical expenses is to avoid the risk factors for VI-AKI. When VI-AKI occurs, targeted treatment and avoidance of risk factors are recommended. In our study, 40.2% of elderly VI-AKI patients did not receive any targeted treatment after the occurrence of this condition, which suggests that clinicians need to be more vigilant about the development of VI-AKI.

Our study analysed the risk factors for death and renal function outcomes in elderly VI-AKI patients. It showed that payment methods (basic national medical insurance or self-financing) were independent protective factors for death, but independent risk factors for renal outcome in VI-AKI patients. Basic national medical insurance is a national health insurance policy in China, and patients covered by Medicare can be reimbursed for part of their medical expenses. Medical expenses are an important factor in patient outcome. An increased investment in health insurance will be conducive to the patient recovery. However, in our study, payment methods showed the opposite influence on death and renal outcome in VI-AKI patients. This may have been due to the small sample size, and further studies, with larger sample sizes, should be carried out to confirm this finding. The presence of diabetes and serum albumin level reflected patients' physical condition, and were independent risk factors for death. This suggests that more attention should be paid to patients with diabetes, and that low serum albumin levels should be avoided. CHD was an independent risk factor for renal outcome in VI-AKI patients, which also warrants attention. Concomitant drugs also had an effect on the outcome of AKI; concomitant metronidazole/ornidazole or steroids were independent risk factors for death and concomitant contrast medium was an independent risk factor for renal outcome. Therefore, when AKI occurs, alternative drugs should be chosen and the patient should be monitored carefully. However, as our sample size was relatively small and the specific mechanisms for these associations with outcomes for VI-AKI patients are unclear, there is clearly a need for a larger prospective study, and also further mechanistic studies.

The strengths of the present study were as follows. First, it examined a large population of elderly Chinese patients, and there have been few studies on risk factors for AKI in this population previously. Secondly, our survey analysed not only the condition of AKI and its associated risk factors, but also its treatment and outcomes. We identified risk factors for VI-AKI, to support its prevention and management. Thirdly, our study analysed 41 types of drugs used concomitantly with VAN treatment, which is a large number; the diversity of drugs examined was greater than that in most previous studies, and this was the first study to examine the concomitant use of Chinese patent drugs in elderly Chinese patients. However, the study also had several limitations. First, this was a single-centre retrospective study. Secondly, we lacked VAN therapeutic concentrations due to the low TDM rate and lower rate of patients whose VAN though serum concentrations were obtained at the correct time in clinical practice. Thirdly, our study did not analyse plasma VAN concentrations as a risk factor for AKI. Finally, our study did not analyse the financial costs associated with AKI.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years

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Contributors

P.K., L.X. and L.Q. designed the research. P.K and W.Y. analysed the data. P.K. wrote the manuscript. P.K., C.Z., X.J., C.L., X.Q., W.W. and D.P. gave final approval of the version to be published.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13594/suppinfo

Table S1 Cause of shock
Table S2 The severity of vancomycin-induced acute kidney injury