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Association of vancomycin plus piperacillin–tazobactam with early changes in creatinine versus cystatin C in critically ill adults: a prospective cohort study

Todd A. Miano[1,2,3*], Sean Hennessy[1,2,3], Wei Yang[1,2,3], Thomas G. Dunn[4], Ariel R. Weisman[4], Oluwatosin Oniyide[4], Roseline S. Agyekum[4], Alexandra P. Turner[4], Caroline A. G. Ittner[4], Brian J. Anderson[4], F. Perry Wilson[5], Raymond Townsend[6], John P. Reilly[4], Heather M. Giannini[4], Christopher V. Cosgriff[4], Tiffanie K. Jones[4], Nuala J. Meyer[4] and Michael G. S. Shashaty[3,4]

Abstract

Purpose: Although dozens of studies have associated vancomycin + piperacillin–tazobactam with increased acute kidney injury (AKI) risk, it is unclear whether the association represents true injury or a pseudotoxicity characterized by isolated effects on creatinine secretion. We tested this hypothesis by contrasting changes in creatinine concentration after antibiotic initiation with changes in cystatin C concentration, a kidney biomarker unaffected by tubular secretion.

Methods: We included patients enrolled in the Molecular Epidemiology of SepsiS in the ICU (MESSI) prospective cohort who were treated for ≥ 48 h with vancomycin + piperacillin–tazobactam or vancomycin + cefepime. Kidney function biomarkers [creatinine, cystatin C, and blood urea nitrogen (BUN)] were measured before antibiotic treatment and at day two after initiation. Creatinine-defined AKI and dialysis were examined through day-14, and mortality through day-30. Inverse probability of treatment weighting was used to adjust for confounding. Multiple imputation was used to impute missing baseline covariates.

Results: The study included 739 patients (vancomycin + piperacillin–tazobactam $n = 297$, vancomycin + cefepime $n = 442$), of whom 192 had cystatin C measurements. Vancomycin + piperacillin–tazobactam was associated with a higher percentage increase of creatinine at day-two 8.04% (95% CI 1.21, 15.34) and higher incidence of creatinine-defined AKI: rate ratio (RR) 1.34 (95% CI 1.01, 1.78). In contrast, vancomycin + piperacillin–tazobactam was not associated with change in alternative biomarkers: cystatin C: − 5.63% (95% CI − 18.19, 8.86); BUN: − 4.51% (95% CI − 12.83, 4.59); or clinical outcomes: dialysis: RR 0.63 (95% CI 0.31, 1.29); mortality: RR 1.05 (95%CI 0.79, 1.41).

*Correspondence: tmiano81@gmail.com
[1] Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, 423 Guardian Drive, 809 Blockley Hall, Philadelphia, PA 19104, USA
Full author information is available at the end of the article

Nuala J. Meyer and Michael G. S. Shashaty contributed equally in the senior author role.

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Conclusions: Vancomycin + piperacillin–tazobactam was associated with creatinine-defined AKI, but not changes in alternative kidney biomarkers, dialysis, or mortality, supporting the hypothesis that vancomycin + piperacillin–tazobactam effects on creatinine represent pseudotoxicity.

Keywords: Vancomycin, piperacillin–tazobactam, Acute kidney injury, Cystatin C, Nephrotoxicity, Sepsis

Introduction

Vancomycin (VN) and piperacillin–tazobactam (PT) are two cornerstones of antibiotic therapy in acutely ill patients with sepsis. In a recent analysis of 576 United States hospitals, these agents were the two most commonly used antibiotics, accounting for over 13 million days of antibiotic therapy in 2016 [1]. Given the key role of this antibiotic combination, the emergence of evidence linking VN + PT to acute kidney injury (AKI) is a major drug safety concern [2, 3]. Nearly fifty observational studies have demonstrated this association, with a recent meta-analysis suggesting VN + PT increases AKI risk two-fold [4]. In response to these data, some health systems have implemented large-scale initiatives to avoid the combination [2, 3].

Despite this epidemiologic evidence, the mechanism of potential interaction is unknown. VN can cause acute tubular necrosis via oxidative stress and the formation of obstructive tubular casts [5, 6]. In contrast, there is little evidence linking PT to nephrotoxicity, other than rare cases of acute interstitial nephritis [7]. Moreover, animal models have failed to demonstrate synergistic toxicity [6, 8–10], with some suggesting that PT may actually reduce VN nephrotoxicity [8–10].

The literature supporting the AKI association in humans is based on creatinine-defined AKI [4, 11]. Serum creatinine, the standard kidney function biomarker, is subject to proximal tubular secretion, which accounts for 10–40% of creatinine clearance in healthy adults and up to 60% in patients with chronic kidney disease (CKD) [12]. Notably, both VN and PT bind to renal transporters that mediate creatinine secretion [13–19]. Thus, the association with creatinine defined AKI may represent pseudotoxicity, mediated by effects on tubular secretion of creatinine without toxic effects on kidney parenchyma.

The uncertain nature of the AKI association has created a major dilemma for bedside clinicians and health system antimicrobial stewardship programs: if VN + PT is truly nephrotoxic, the combination may contribute substantially to AKI and associated downstream effects including heightened risks of CKD, cardiovascular disease, and mortality [20, 21]; if not, avoidance of the combination could limit treatment of life-threatening infections, expose patients to toxicity from alternative antibiotics, and worsen antimicrobial resistance patterns [3, 22–24]. We thus aimed to examine the creatinine secretion hypothesis by contrasting changes in creatinine after antibiotic initiation with changes in cystatin C (Cys-C), a well-validated biomarker of kidney function that is unaffected by tubular secretion [25, 26]. We hypothesized that VN + PT would be associated with changes in creatinine, but not associated with changes in cystatin C, need for dialysis, or mortality, findings that would support the premise that VN + PT-associated creatinine changes do not reflect changes in kidney function or underlying tissue injury. Parts of this work were presented in abstract form at the 2021 American Thoracic Society conference [27].

Take-home message

Vancomycin plus piperacillin–tazobactam was associated with an increased risk of creatinine-defined acute kidney injury, but not changes in alternative kidney function biomarkers (cystatin C, blood urea nitrogen), or downstream clinical outcomes associated with true acute kidney injury (dialysis or mortality). These findings suggest that the association of vancomycin + piperacillin–tazobactam with creatinine-defined acute kidney injury may represent pseudotoxicity

Methods

Design and population

This study was part of the Molecular Epidemiology of SepsiS in the ICU (MESSI) project [28], an ongoing prospective observational study that enrolls patients admitted to the intensive care unit (ICU) with severe sepsis or septic shock meeting sepsis-2 criteria [29]. MESSI exclusion criteria are a lack of commitment to life-sustaining measures or unwillingness to provide consent. We identified MESSI patients treated with VN + PT or VN + cefepime (CP) for ≥ 48 h, with each drug initiated within ± 48 h of ICU admission (the antibiotic cohort). We chose CP as the comparator because it's commonly used for empiric sepsis treatment, and when combined with VN, has been associated with lower AKI risk compared to VN + PT [30, 31]. The index date was the date and time of concomitant antibiotic initiation. We excluded patients from the antibiotic cohort for end stage renal disease, dialysis within 14 days before the index date, or baseline AKI, defined as an index creatinine ≥ 1.5

times higher than baseline creatinine. Index creatinine was the last value obtained before the index date. Baseline creatinine was the average of outpatient or hospital discharge creatinine values from 365 days before to 7 days before hospital admission [32]. Where these data were missing, baseline was defined as the lowest value within seven days before ICU admission.

Outcomes

Primary outcomes were kidney function biomarker concentrations (creatinine and Cys-C) measured at index and at day two (48–72 h) after combination antibiotic initiation (Fig. 1). We chose Cys-C because it is a validated kidney function biomarker [26] that does not undergo tubular secretion [25], and has been shown to identify AKI earlier than creatinine in patients with sepsis [33, 34]. Cys-C was measured with electrochemiluminescence from stored plasma biospecimens [35]. We included patients in the Cys-C analyses (i.e., the Cys-C sub-cohort) if the timing of their blood draws aligned with a priori defined windows for baseline and follow-up Cys-C measurement (Fig. 1). The protocol for collection and storage of plasma samples is described in the appendix, and details of plasma sample availability are shown in Table S1. Serum creatinine concentrations between index and day two were obtained from Penn's electronic health record (EHR) database for all patients in the antibiotic cohort. For the subset of patients included in the Cys-C cohort, we used clinical creatinine measurements that were obtained closest in time to the plasma sample

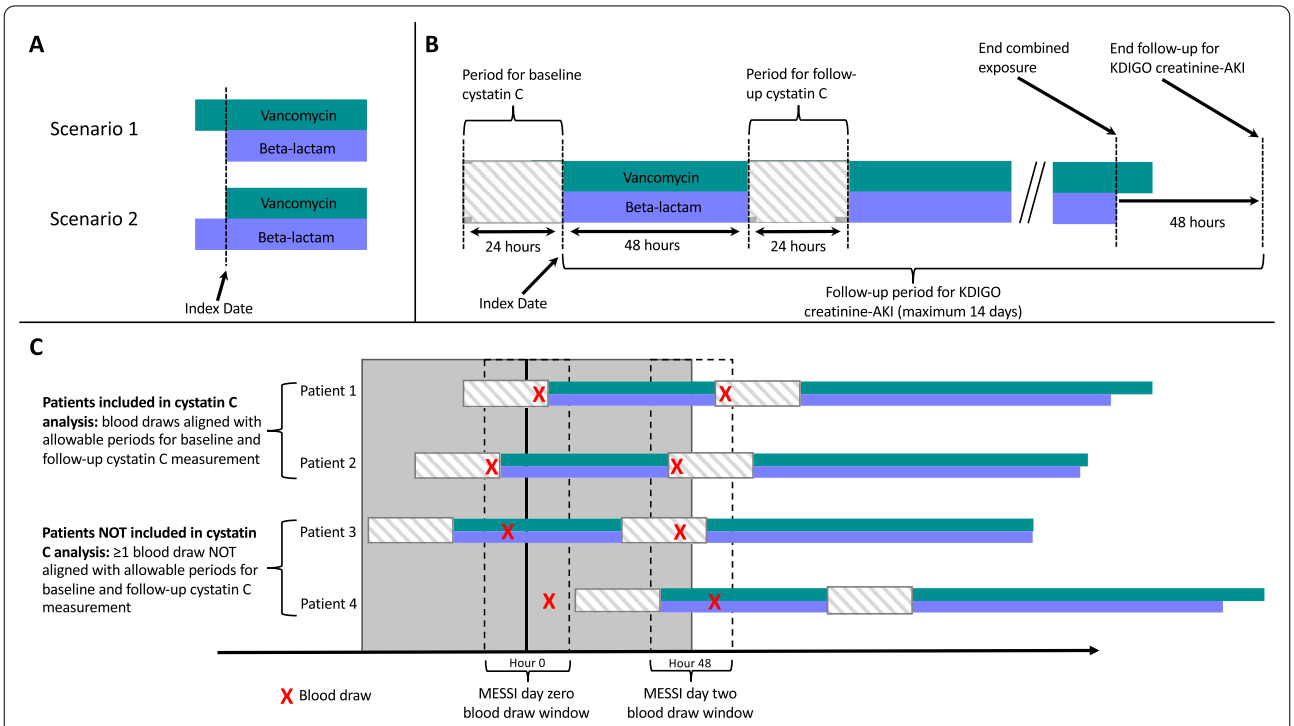

Fig. 1 Framework for patient inclusion, index date, and follow-up for measures of kidney function. The figure shows follow-up definitions during combined exposure to vancomycin (teal bars) and a beta-lactam (light blue bars, either piperacillin–tazobactam or cefepime). **A** Two scenarios by which patients could enter the antibiotic cohort. For both scenarios, the index date was defined as the date and time when combined therapy started. **B** Time frame, with respect to antibiotic exposure, for measurement of kidney function markers at baseline and during follow-up. The period for baseline cystatin C measurement was the 24 h period immediately prior to the index date. The period for follow-up cystatin C measurement was the period from 48 to 72 h after the index date. For direct comparative analyses with cystatin C, change in serum creatinine was measured over the same time frame. Follow-up for KDIGO defined acute kidney injury (AKI) began on the index date and continued until: lapse in concomitant antibiotic exposure > 48 h, hospital discharge, death, or 14 days after the index date. We followed AKI episodes for 7 days after onset to assess severity stage and initiation of renal replacement therapy. Follow-up for mortality began on the index date and continued until death or until 30 days after the index date. **C** Alignment of antibiotic follow-up with the underlying time-line of the MESSI cohort study. Patients were included in cystatin C analyses if the timing of their blood draws aligned with the allowable time periods for baseline and follow-up cystatin C measurement (hashed gray-white boxes) as defined in **B**. The vertical solid black line denotes ICU admission (MESSI hour zero) and the gray shaded box is the period around MESSI hour zero during which eligible antibiotic courses had to be initiated (±48 h). MESSI day zero plasma samples (red X) were obtained from residual citrated plasma collected at emergency department presentation, or for patients transferred from the hospital ward, at the point closest to ICU admission (dashed vertical lines around hour zero). Follow-up residual plasma was obtained approximately 48 h after ICU admission (dashed vertical lines around hour 48)

used to measure Cys-C. For antibiotic cohort patients not included in the Cys-C cohort (Fig. 1c), we randomly selected both index and day two creatinine values from those measured clinically during the baseline and follow-up time periods (Fig. 1b).

Because Cys-C was not available for all patients in the antibiotic cohort, we examined blood urea nitrogen (BUN) as a secondary biomarker (obtained from the EHR as creatinine above) of glomerular filtration that is not subject to tubular secretion [36]. Lastly, to quantitatively test the hypothesis that the change in creatinine after antibiotic initiation differs from the change in comparator biomarkers, we calculated ratios of Cys-C concentration:creatinine concentration and BUN concentration:creatinine concentration at baseline and day two.

Secondary clinical outcomes were creatinine-defined AKI though day 14, dialysis, and 30-day mortality (Fig. 1). AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria [37], with index creatinine used as the reference for phenotyping.

Data collection

MESSI personnel collected plasma biospecimens, demographics and comorbidity variables. Medications, laboratory values, and dialysis orders were obtained via EHR query. Potential confounders were selected a priori based on clinical knowledge and prior literature, including factors associated with AKI, severity of illness, or potential non-renal determinants of cystatin C concentration (Table 1, Table S2) [38–40]. Concomitant medication and laboratory variables were assessed during the 24 h before the index date. For each laboratory measure, the value most proximate to cohort entry was collected. Dosing of VN, PT, and CP was calculated from doses administered during the first 24 h after the index date (see Table S3 for details).

Data analysis

Descriptive statistics and missing data

Baseline covariate balance was examined using standardized mean differences (SMD), with absolute SMD values > 0.1 indicative of imbalance [41]. Missing values were observed for several baseline laboratory and vital sign measures (Table S4). We imputed missing data using multiple imputation, producing fifty imputation data sets (see appendix for details). We estimated time to KDIGO defined AKI with Kaplan–Meier curves.

Inverse probability of treatment weighting

We adjusted for confounding using inverse probability of treatment weights (IPTW), calculated from the propensity score for VN + PT treatment. IPTW analysis was applied to the multiply imputed datasets using the within-imputation method [42], wherein propensity score estimation and weighted outcome modeling is repeated separately in each dataset, then combined using standard methods (Figure S1). Propensity scores were estimated using logistic regression conditional on covariates listed in Table 1 (antibiotic cohort) and Table S2 (Cys-C sub-cohort). Propensity scores were estimated separately in the antibiotic cohort and the Cys-C subcohort to ensure correct propensity score model specification. Covariates showing residual imbalance after IPTW were included in weighted outcome models.

Outcome models

We modeled day two kidney function biomarkers using IPTW linear regression, adjusted for baseline biomarker concentration [43]. We log-transformed biomarker concentrations for analysis and exponentiated model coefficients to provide the percentage difference between groups. Secondarily, we examined the change in biomarker concentrations at day two as dichotomous variables, comparing the incidence of ≥ 50% increases in biomarker concentrations from baseline to day two with IPTW Poisson regression models. Analysis of day two creatinine and BUN concentrations were conducted in the Cys-C sub-cohort, and secondarily in the full antibiotic cohort (to examine consistency of results in the Cys-C subcohort compared to those from the antibiotic cohort). IPTW Poisson regression was also used to model incidence rate ratios (IRR) for KDIGO defined AKI, dialysis, and mortality.

Sensitivity analysis

Sensitivity analyses included: (1) repeating all models after restricting to patients with overlapping propensity scores (to examine the impact of positivity assumption violations) [44]; (2) repeating all models after restricting to patients with propensity scores between the 1st and 99th percentiles of the overlapping propensity scores (to examine potential unmeasured confounding in the tails of the propensity score distributions) [44]; (3) repeat analysis of day two Cys-C concentrations after excluding patients treated with corticosteroids (to examine potential confounding by corticosteroid exposure); (4) repeat analysis of KDIGO defined AKI after restricting follow-up to 7 days; (5) repeating analyses with additional adjustment for calendar year (to examine potential confounding from practice changes over time); and (6) analysis of the incidence of BUN increases ≥ 50% from baseline through day 14 (to examine consistency of day two analysis with results from later time points).

Table 1 Baseline characteristics before and after weighting in antibiotic cohort

Variable	Unweighted Cohort[a]			Weighted Cohort[a]		
	VN + CP ($n = 442$[b])	VN + PT ($n = 297$[b])	SMD	VN + CP ($n = 369$[c])	VN + PT ($n = 370$[c])	SMD[d]
Demographics						
Age, years, mean	60.6	61.8	0.079	61.5	61.5	0.007
Male sex, %	54.3	56.6	0.046	55.6	54.8	0.019
Race, %						
White	64.9	67	0.044	65.8	68.6	0.058
Black	28.1	26.3	0.040	27.6	25.9	0.037
Asian	3.6	4	0.022	3.6	3.3	0.015
Other	3.4	2.7	0.041	3.0	2.2	0.046
BMI, mean	27.6	27.1	0.063	27.3	27	0.035
Admission characteristics						
Admission source, %						
ED	55.7	46.5	0.185	52.1	50.1	0.038
Ward	36	45.5	0.194	39.9	41.9	0.041
OSH	8.4	8.1	0.011	8.1	8	0.007
Mechanical ventilation, %	41.9	45.5	0.073	44.2	41.5	0.055
APACHE III, mean	84.4	89.5	0.155	88	86.2	0.054
MAP, mmHG, mean	81.4	80.1	0.078	80.8	81	0.013
Heart beats per minute, mean	103.8	102.7	0.051	102.7	102.7	0.007
Temperature, °F, mean	99.1	98.7	0.239	98.9	98.9	0.017
Respirations per minute, mean	23.7	23	0.103	23.4	23.2	0.023
Kidney function						
Index creatinine, mg/dL, mean	1.1	1.1	0.081	1.1	1.1	0.011
Index eGFR[e], ml/min, mean	79.6	76.4	0.094	78.7	77.1	0.047
Index GFR categories, %						
eGFR ≥ 120 ml/min	10.9	9.4	0.047	9.7	9.3	0.014
eGFR 90–119 ml/min	32.6	29	0.079	33.3	30.2	0.066
eGFR 60–89 ml/min	25.6	27.3	0.039	24.6	26	0.032
eGFR 30–59 ml/min	23.5	24.9	0.032	23.5	25.1	0.037
eGFR < 30 ml/min	7.5	9.4	0.071	8.9	9.4	0.017
Infection characteristics						
Vancomycin dose[f], mg/kg, mean	30.7	30.5	0.016	30.3	30.6	0.021
Infection source, %						
Pulmonary	59.3	57.2	0.041	58.4	61.4	0.060
Abdominal	10	13.8	0.119	10.7	9.9	0.026
Genitourinary	7.7	7.4	0.011	8.4	8.6	0.010
Blood	7.5	6.4	0.042	6.9	6.2	0.026
SSTI/Bone	3.8	7.1	0.142	5	4.9	0.005
Unclear/Unknown	11.8	8.1	0.123	10.6	9.1	0.051
Comorbidities						
Heart failure, %	14.7	12.8	0.056	14	13.4	0.018
Diabetes mellitus, %	26	31	0.110	27.5	27.9	0.012
Hypertension, %	52.3	52.9	0.012	52.2	50.8	0.030
Chronic kidney disease, %	12.2	11.8	0.013	11.8	13.5	0.052
Cirrhosis, %	5.7	12.1	0.229	7.4	7.8	0.015
Metastatic solid cancer, %	15.2	21.5	0.166	16.9	16.4	0.011
Leukemia, %	15.4	9.1	0.193	13.6	15.1	0.044
Lymphoma, %	11.3	4.4	0.260	8.4	7.5	0.033

Table 1 (continued)

Variable	Unweighted Cohort[a]			Weighted Cohort[a]		
	VN + CP ($n = 442$[b])	VN + PT ($n = 297$[b])	SMD	VN + CP ($n = 369$[c])	VN + PT ($n = 370$[c])	SMD[d]
Myeloma, %	4.5	2.7	0.098	3.8	4.1	0.020
Solid organ transplant, %	10.2	7.4	0.098	9	8.4	0.024
Laboratory values						
WBC, $\times 10^8$ cells/L, mean	10.8	14.1	0.265	12.5	12.2	0.027
Hemoglobin, g/dL, mean	9.9	9.9	0.033	9.9	9.8	0.031
Platelets, $\times 10^{11}$ cells/L, mean	174.3	204.5	0.217	187.3	187.6	0.014
Albumin, g/dL, mean	2.8	2.6	0.303	2.7	2.8	0.038
Bicarbonate, mEq/L, mean	23.7	22.8	0.181	23.5	23.5	0.011
Chloride, mEq/L, mean	104.8	104.8	0.001	104.9	104.9	0.009
BUN, mg/dL, mean	23.3	26.1	0.154	24.6	24.9	0.017
Calcium, mg/dL, mean	8.2	8.1	0.065	8.2	8.2	0.010
Magnesium, mg/dL, mean	1.8	1.8	0.008	1.8	1.8	0.022
Bilirubin, mg/dL, mean	1.4	2.7	0.319	1.8	1.8	0.018
Lactate, mmol/L, mean	2	2.3	0.138	2.1	2	0.024
Medications						
Aminoglycosides, %	24.9	26.6	0.039	24.5	23.5	0.023
NSAIDs, %	6.1	6.4	0.012	6.5	6.6	0.007
Calcineurin inhibitors, %	9.5	6.4	0.115	8.6	9.4	0.031
Loop diuretics, %	9.5	13.1	0.115	11.3	11.8	0.016
Trimethoprim/Sulfamethoxazole, %	11.1	7.7	0.115	9.7	8.6	0.042
Proton pump inhibitor, %	39.1	43.1	0.080	40.4	41.5	0.023
RAS inhibitor, %	7.2	5.1	0.091	6.3	6.4	0.019
Beta-blocker, %	17	16.8	0.004	16.4	16.9	0.015
Calcium channel blocker, %	9.3	7.4	0.068	8.6	8.7	0.014
Other antihypertensive, %	9.7	5.7	0.150	8.4	8.7	0.020
Stress-dose corticosteroid, %	22.6	24.2	0.038	23.4	22.8	0.014
Other steroids, %	34.8	22.6	0.274	30.2	31.1	0.020

SMD standardized mean difference, *BMI* body mass index, *ED* emergency department, *OSH* outside hospital, *APACHE* Acute Physiology and Chronic Health Evaluation, *MAP* mean arterial pressure, *eGFR* estimated glomerular filtration rate, *SSTI* skin and soft tissue infection, *WBC* white blood cell, *BUN* blood urea nitrogen, *NSAID* nonsteroidal antiinflammatory drug, *RAS* renin–angiotensin system, *VN + PT* vancomycin + piperacillin–tazobactam, *VN + CP* vancomycin + cefepime

[a] To facilitate comparisons of the unweighted and weighted population, the table shows means without standard deviation and percentages without counts

[b] Actual sample size

[c] Effective sample size after inverse probability of treatment weighting

[d] Overall SMDs were obtained after weighting by taking the average of weighted SMDs calculated separately in each of the imputation datasets

[e] Estimated glomerular filtration rate was calculated using the CKD-Epidemiology equation

[f] Vancomycin dose calculated from doses administered during the first 24 h after the index date

Results

Study population

The study included 739 patients in the antibiotic cohort, 192 of whom had plasma samples for Cys-C analysis (Fig. 2). Patients in the Cys-C sub-cohort had similar baseline kidney function, severity of illness scores, and need for mechanical ventilation compared to patients without Cys-C samples (Table S7). Patient characteristics are shown in Table 1 (antibiotic cohort) and table S2 (Cys-C sub-cohort). Before weighting, VN + PT patients had higher severity of illness scores, lower baseline eGFR, higher lactate concentration, and more frequent diabetes mellitus and cirrhosis. Weighting balanced covariates in both cohorts. In the Cys-C sub-cohort, there was minor residual imbalance in respiratory rate, hypertension, cancer, and solid organ transplant; these covariates were included in the weighted outcome models.

Kidney function biomarkers at day two

VN + PT was associated with significantly higher average creatinine concentrations (Table 2) and a higher frequency

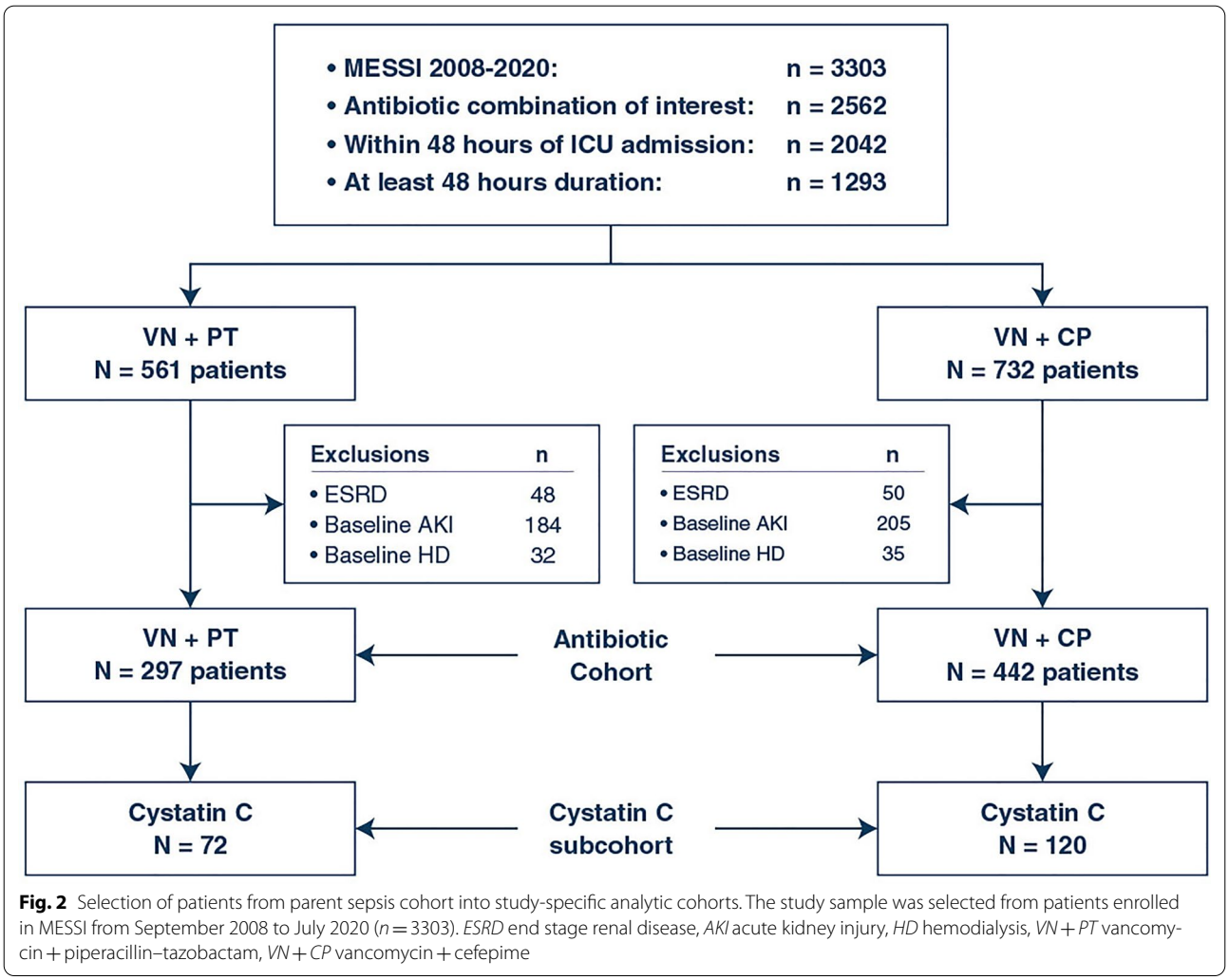

Fig. 2 Selection of patients from parent sepsis cohort into study-specific analytic cohorts. The study sample was selected from patients enrolled in MESSI from September 2008 to July 2020 ($n = 3303$). *ESRD* end stage renal disease, *AKI* acute kidney injury, *HD* hemodialysis, *VN + PT* vancomycin + piperacillin–tazobactam, *VN + CP* vancomycin + cefepime

of creatinine increases of ≥ 50% (Table 3). In contrast, VN + PT was associated with non-significantly lower average Cys-C concentrations and a similar frequency of Cys-C increases of ≥ 50% compared to VN + CP. BUN measures did not differ significantly between groups at day two, nor did the rate of ≥ 50% increases of BUN through day 14 (Table S8). Lastly, both the Cys-C:creatinine ratio and BUN:creatinine ratio were significantly lower in the VN + PT group vs. the VN + CP group, indicating that creatinine increased to a significantly greater extent than either Cys-C or BUN by day two (Table 2).

Clinical outcomes

The time to KDIGO-defined AKI is shown in Figure S4. Crude and weighted clinical outcome analyses are shown in Table 4. VN + PT was associated with a significantly higher rate of creatinine-defined AKI at day-14. The association was attenuated and non-significant when restricting to stage 2 or higher events. Similarly, VN + PT was not associated with the rate of dialysis or mortality after weighting.

Sensitivity analyses

Results were minimally changed by propensity score trimming (Table S9, Table S10), or adjustment for calendar year (Table S11). Cys-C results were similar after excluding corticosteroid exposed patients (Table S12). Lastly, the 7-day analysis of KDIGO-AKI provided similar results to the 14-day analysis (Table S13).

Discussion

VN + PT was associated with increased creatinine concentrations at day two and an increased rate of creatinine-defined AKI at day 14. In contrast, VN + PT was not associated with changes in Cys-C or BUN at day two. We further observed that VN + PT-associated AKI

Table 2 Percentage difference in kidney function biomarker concentrations at day two

	Cystatin C Cohort ($n=192$)			Antibiotic Cohort ($n=739$)		
	VN + CP	VN + PT	% Difference[a]	VN + CP	VN + PT	% Difference[a]
Cystatin C, mg/L, mean (SD)						
Crude	1.52 (1.22)	1.51 (1.33)	− 1.26 (− 17.36, 17.97)	–	–	–
IPTW			− 5.63 (− 18.19, 8.86)			–
Cystatin C:Creatinine ratio, mean (SD)[b]						
Crude	1.49 (0.83)	1.23 (0.66)	− 17.57 (− 28.92, − 4.41)	–	–	–
IPTW			− 13.65 (− 24.52, − 1.23)			–
Creatinine, mg/dL, mean (SD)						
Crude	1.15 (0.9)	1.46 (1.19)	19.79 (− 1.05, 45.01)	1.16 (0.86)	1.35 (0.93)	17.8 (7.6, 28.9)
IPTW			9.96 (− 3.19, 24.90)			8.04 (1.21, 15.34)
BUN, mg/dL, mean (SD)						
Crude	27.6 (21.2)	26.9 (19.5)	− 3.97 (− 22.96, 19.69)	25.9 (20.7)	27.0 (18.9)	6.91 (− 4.22, 19.33)
IPTW			− 9.05 (− 23.72, 8.45)			− 4.51 − 12.83, 4.59)
BUN:Creatinine ratio, mean (SD)[b]						
Crude	23.8 (11.9)	21.5 (10.9)	− 9.24 (− 15.99, − 1.99)	25.5 (13.1)	20.4 (9.5)	− 19.83 (− 30.82, − 7.10)
IPTW			− 12.16 (− 17.35, − 6.66)			− 17.86 (− 27.54, − 6.72)

VN + PT vancomycin + piperacillin–tazobactam, *VN + CP* vancomycin + cefepime

[a] Comparison of biomarker concentrations at day two, adjusted for baseline concentration. Biomarker concentrations were log-transformed for analysis and model coefficients were exponentiated to provide the percentage difference between groups

[b] Values below one indicate creatinine increased to a greater extent than comparator biomarker (Cys-C or BUN)

Table 3 Rates of ≥ 50% increases of kidney function biomarkers at day two

	Cystatin C Cohort ($n=192$)			Antibiotic Cohort ($n=739$)		
	VN + CP	VN + PT	Rate ratio[a]	VN + CP	VN + PT	Rate ratio[a]
≥ 50% increase cystatin C, *n* (%)						
Crude	17 (14.2)	14 (19.4)	1.37 (0.72, 2.61)	–	–	–
IPTW			0.95 (0.44, 2.02)			–
≥ 50% increase creatinine, *n* (%)						
Crude	10 (8.3)	14 (19.4)	2.33 (1.09, 4.97)	43 (9.7)	54 (18.2)	1.87 (1.29, 2.71)
IPTW			1.86 (0.85, 4.09)			1.55 (1.02, 2.34)
≥ 50% increase BUN, *n* (%)						
Crude	27 (22.5)	19 (26.4)	1.17 (0.70, 1.95)	90 (20.4)	63 (21.2)	1.04 (0.78, 1.38)
IPTW			0.99 (0.57, 1.75)			0.88 (0.63, 1.23)

VN + PT vancomycin + piperacillin–tazobactam, *VN + CP* vancomycin + cefepime

[a] Rate ratio estimated from Poisson regression accounting for person-time at risk

did not translate into higher dialysis or mortality rates. Taken together, these findings suggest that the association with AKI represents pseudotoxicity, and that avoidance of this essential antibiotic combination may be unwarranted.

To our knowledge, this is the first study of VN + PT to employ Cys-C as an alternative to creatinine, which allowed us to conduct the most direct mechanistic assessment of the VN + PT interaction in humans to date. Cys-C is a validated biomarker of kidney function that has a shorter half-life than creatinine [25]. Thus, the absence of any discernable effect of VN + PT on Cys-C concentrations at day two suggests that the significant increases in creatinine over that time period were not associated with underlying changes in kidney function. VN + PT also showed no association with changes in BUN, an additional kidney biomarker that does not undergo tubular secretion. These consonant findings, as well as the consistency of BUN and creatinine analyses between the Cys-C subcohort and the full antibiotic

Table 4 Clinical outcomes

	VN + CP	VN + PT	Rate ratio[a]
KDIGO-AKI at 14 days, *n* (%)			
Crude	129 (29.2)	125 (42.1)	1.59 (1.25, 2.04)
IPTW			1.34 (1.01, 1.77)
KDIGO-AKI stage 2/3 at 14 days, *n* (%)			
Crude	67 (15.2)	60 (20.2)	1.47 (1.04, 2.09)
IPTW			1.10 (0.73, 1.67)
AKI requiring dialysis at 14 days, *n* (%)[b]			
Crude	26 (5.9)	14 (4.7)	0.89 (0.46, 1.69)
IPTW			0.63 (0.31, 1.29)
Mortality at 30 days, *n* (%)			
Crude	151 (34.2)	136 (45.8)	1.53 (1.21, 1.92)
IPTW			1.05 (0.79, 1.41)

VN + PT vancomycin + piperacillin–tazobactam, *VN + CP* vancomycin + cefepime

[a] Rate ratio estimated from Poisson regression accounting for person-time at risk

[b] AKI events occurring through day 14 were followed for 7 days from the onset of AKI to observe for dialysis initiation

cohort, suggest that the Cys-C results are not due to selection bias.

Both piperacillin and tazobactam are substrates for organic anion transporters that have been implicated in the tubular handling of creatinine (OAT1, OAT3) [11, 13, 14, 17, 18]. In addition, VN suppresses OAT1 and OAT3 expression [11, 15, 16]. Thus, competitive inhibition of creatinine secretion and VN-mediated transporter suppression seems a plausible mechanism of increased creatinine concentration [11]. Our findings of isolated increases in creatinine that were not matched by changes in either Cys-C or BUN are consistent with this hypothesized mechanism. Our findings are also consistent with animal studies suggesting that PT does not enhance VN toxicity [6, 8–10], with some suggesting that PT may actually reduce VN nephrotoxicity. A caveat to the animal models is that, beyond demonstrating no adverse effect on kidney function, some have also shown that VN + PT does not increase creatinine concentrations [8, 9]. Nevertheless, regardless of mechanism, the data raise doubt that PT enhances VN-mediated nephrotoxicity.

Our analysis of Cys-C was limited to change over the first two days of treatment, which could miss potential delayed toxicity. However, Kaplan–Meier analysis suggests that VN + PT was associated with an excess of creatinine defined AKI events primarily during the first 2–3 days of treatment, in line with the significantly elevated average creatinine concentrations observed at day two. This pattern is consistent with inhibition of creatinine secretion, which would likely manifest shortly after drug initiation, as creatinine transporter inhibition happens rapidly. Given that cystatin C has a shorter half-life compared to creatinine, it seems unlikely that the early rise in creatinine reflects underlying parenchymal injury that would only manifest delayed Cys-C elevations. In addition, VN + PT was not associated with BUN changes through day-14. Taken together, these data suggest that the day two analysis of Cys-C captures the key time period during which VN + PT mediated its effects.

Based on the magnitude of creatinine change observed with other drugs affecting creatinine secretion (0.2–0.5 mg/dL) [11], creatinine-defined AKI via this mechanism should generally be associated with stage 1 episodes, reflecting relatively small increases in creatinine. We observed a substantially attenuated association between VN + PT and creatinine-defined AKI when analysis was restricted to stage 2 or higher AKI, and no association between VN + PT and patient centered outcomes such as dialysis or mortality, consistent with previous studies [45–47]. Schreier found no association between short courses of VN + PT and stage 2 or higher AKI, dialysis, or mortality at 60 days [45]. Similarly, Buckley showed a significant association between VN + PT and stage 1 AKI, but not stage 2 or stage 3, dialysis, or mortality [46]. Lastly, although Blevins et al. observed significant associations between VN + PT and all AKI stages, this did not translate into higher dialysis or mortality rates [47]. In contrast, Cote observed a significant association between VN + PT and higher risk of dialysis [48]. However, they examined dialysis events that occurred within 30 days of antibiotic initiation, regardless of antibiotic duration or the timing of AKI onset. Thus, it's unclear whether dialysis initiation was attributable to drug exposure. Our study examined dialysis initiated within seven days of AKI events that occurred during antibiotic exposure, targeting events that could plausibly be attributable to drug exposure. In sum, the preponderance of evidence suggests that any potential interaction between VN + PT has limited impact on patient centered outcomes.

Only one other study has examined the VN + PT association with a biomarker other than creatinine. Kane-Gill et al. examined cell cycle arrest markers (tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 [TIMP-2]·[IGFBP7]) in patients who received VN alone, PT alone, or VN + PT [49]. They showed that urinary [TIMP-2]·[IGFBP7] concentrations on the day after antibiotic initiation were higher for VN + PT vs. PT alone, but not different compared to VN alone. However, the analysis was not adjusted for baseline [TIMP-2]·[IGFBP7] concentration [43]. Moreover, it's difficult to know whether the result represents an interaction between VN + PT, the effect of VN alone,

or differences in underlying severity of illness between patients treated with monotherapy versus combination therapy.

Strengths of our study include the prospective study design, extensive confounding adjustment, and multiple imputation of missing data. Our study also has limitations. First, Cys-C concentrations can be affected by body mass index, corticosteroids, thyroid activity, cancer, diabetes mellitus, and solid organ transplant [25, 40]. We mitigated confounding from these factors through IPTW analysis. IPTW balances the distribution of these factors such that their effect would influence Cys-C to a similar extent in both groups. Second, we only had Cys-C concentrations for a subset of patients. However, we showed that the Cys-C subcohort had similar characteristics to the full antibiotic cohort, and supplemented Cys-C with analysis of changes in BUN concentration. Nevertheless, it is important to note that BUN changes can reflect factors other than kidney function; thus, the lack of association with BUN may reflect in part BUN's low specificity for kidney function [36]. Third, the cohort design is susceptible to confounding. We minimized confounding by comparing VN + PT to VN + CP, which is given for the same indication. We controlled for an extensive set of covariates and showed that our results were minimally changed by propensity score trimming, suggesting that confounding from propensity score misspecification is minimal. Further, because risk factors for mortality and AKI overlap substantially, and differences in effectiveness between PT and CP are unlikely [3] mortality can be viewed as a negative control outcome [50]. Thus, our finding of a significant crude association between VN + PT and mortality that was nearly completely nullified in weighted analysis suggests that confounding was minimized. Fourth, there were missing data. We minimized missing data bias with multiple imputation, which allowed us to control for additional covariates such as albumin, lactate, and bilirubin that have generally been unaccounted for in studies of VN + PT and AKI. Fifth, we were unable to account for potential dilutional effects of fluid resuscitation. However, such dilution would be expected to impact creatinine, Cys-C, and BUN similarly. Sixth, we did not have urine output data (UOP). However, UOP data are often incomplete, and are susceptible to ascertainment bias, wherein UOP data are more often complete in patients with urinary catheters, which are typically placed in patients with high severity of illness. Seventh, given the low dialysis rate, our study was underpowered for this endpoint. Lastly, we included critically ill patients enrolled at a single center, which may limit generalizability. However, our replication of associations between VN + PT and creatinine suggest that our findings are not unique to our population.

Conclusions

VN + PT was associated with an increased risk of creatinine-defined AKI, but not changes in alternative kidney function biomarkers or clinical outcomes downstream from true AKI, supporting the hypothesis that creatinine-defined AKI during VN + PT may represent pseudotoxicity.

Supplementary Information
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Author details
[1] Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, 423 Guardian Drive, 809 Blockley Hall, Philadelphia, PA 19104, USA. [2] Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. [3] Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. [4] Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. [5] Section of Nephrology and Clinical and Translational Research Accelerator, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA. [6] Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.

Author contributions
TAM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: TAM, MGSS, NJM, SH. Acquisition, analysis, or interpretation of data: TAM, SH, WY, TGD, ARW, OO, RSA, APT, CAGI, BJA, FPW, RT, JPR, HMG, CVC, TKJ, NJM, MGSS. Drafting of the manuscript: TAM. Critical revision of the manuscript for important intellectual content: TAM, SH, WY, TGD, ARW, OO, RSA, APT, CAGI, BJA, FPW, RT, JPR, HMG, CVC, TKJ, NJM, MGSS. Manuscript approval: All authors gave final approval of this version.

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Declarations

Conflicts of interest
FPW received research funding from Boeringher-Ingelheim, Astrazeneca, Vifor pharmaceuticals, and Whoop, Inc. SH leads a research and training center that receives educational funding from Pfizer Inc. MJM received research funding to her institution from Athersys, Inc, Biomarck Inc, and Quantum Leap Healthcare Collaborative for work unrelated to this manuscript. All other authors have nothing to disclose.

Role of the funder/sponsor
The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethics approval
Subjects are enrolled with a waiver of timely informed consent with approval of the institutional review board (IRB) of the University of Pennsylvania (IRB #808542). Subjects or their surrogates are approached as soon as possible for consent, and if consent is not obtained, all biospecimens and data are discarded.

Consent to participate
Subjects are enrolled with a waiver of timely informed consent with approval of the IRB of the University of Pennsylvania (IRB #808542). Subjects or their surrogates are approached as soon as possible for consent, and if consent is not obtained, all biospecimens and data are discarded.

Consent to publish
Not applicable/all data used for the present study have been anonymized, and the submission does not include information that may identify individual persons.

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