Combined vancomycin and piperacillin-tazobactam treatment is not associated with worsening kidney function when assessed using plasma cystatin C

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1. Background

- Dozens of recent studies have shown that combined treatment with vancomycin and piperacillin-tazobactam (VN+PT) is associated with increased risk of acute kidney injury (AKI). The mechanism of this potential drug-drug interaction is unknown.
- Although VN is known to be nephrotoxic, PT has heretofore shown minimal AKI risk, and animal models have shown no evidence of synergistic toxicity. VN and PT are substrates for renal transporters that mediate creatinine secretion, suggesting that creatinine defined AKI might be an artifact of altered creatinine transport without parenchymal injury.
- We tested this hypothesis by contrasting changes in creatinine concentrations after antibiotic initiation with changes in cystatin C (Cys-C) concentrations, a well-validated marker of glomerular filtration rate that is unaffected by tubular secretion

2. Methods

Cohort

- The study included patients enrolled in the Molecular Epidemiology of SepsiS in the ICU [MESSI] cohort study who were treated for ≥48 hours with VN+PT or VN+cefepime (CP), where combination treatment was initiated within 48 hours of ICU admission.
- Exclusion criteria were baseline end stage renal disease and/or need for dialysis, pre-treatment AKI, or baseline creatinine > 4 mg/dL

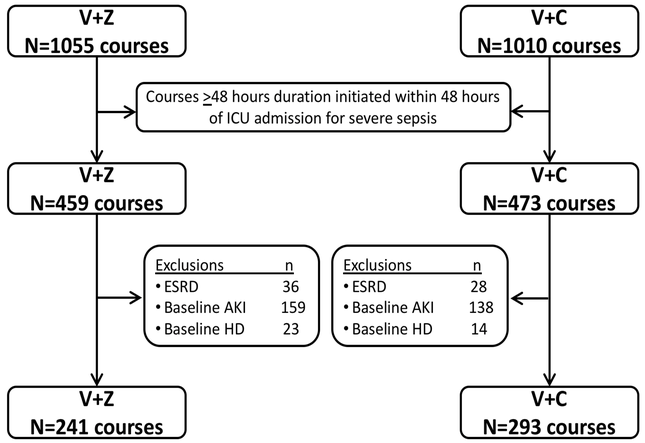
Outcomes

- Changes in kidney function were evaluated by:
  1) the percentage change in Cys-C from baseline to 48 hours
  2) the percentage change in creatinine from baseline to 48 hours
  3) the incidence of AKI at day 14 (defined with KDIGO creatinine criteria)
  4) the incidence of renal replacement therapy (RRT) at day 14.

Analysis

- Balance of baseline characteristics examined with standardized mean differences
- Percentage change in kidney biomarkers estimated with multivariable linear regression
- Relative risk of AKI and RRT estimated with multivariable Poisson regression using robust variance estimation

3. Patient selection

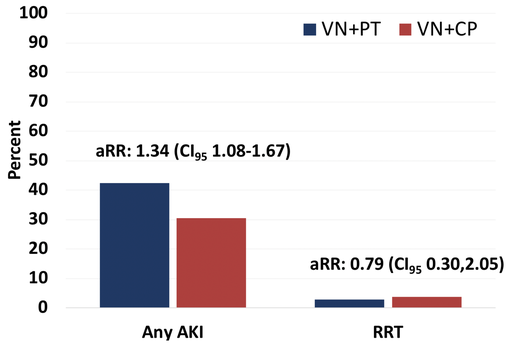


4. Baseline patient characteristics

Variable	VN+PT	VN+CP	SMD
Age, years, mean (SD)	61.5 (14.4)	59.4 (15.7)	0.138
Male sex, (%)	139 (58)	164 (56)	0.034
Race			
White	184 (63)	162 (67)	0.093
Black	79 (27)	65 (27)	0.000
Other	30 (10)	14 (6)	-0.164
Admission source, (%)			
Emergency dept.	159 (66)	214 (73)	-0.154
Ward	60 (25)	52 (18)	0.175
Outside transfer	22 (9.1)	27 (9)	-0.003
APACHE III, mean (SD)	88.4 (31.6)	86.8 (35.3)	0.047
eGFR, ml/min, mean (SD)	76 (34)	83 (35)	-0.213
Nephrotoxins			
Aminoglycosides, (%)	19 (8)	38 (13)	-0.167
Acyclovir	29 (12)	48 (16)	-0.125

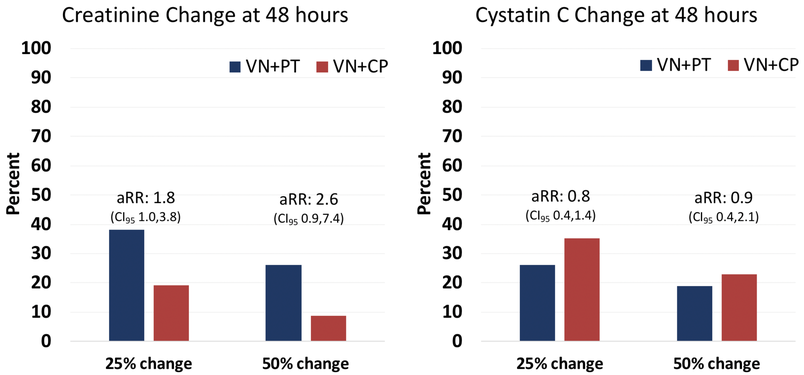
VN+PT- vancomycin and piperacillin-tazobactam; VN+CP- vancomycin and cefepime; SMD- standardized mean difference

5. Incidence of AKI and RRT at 14 days



Adjusted relative risk (aRR) estimated with multivariable Poisson regression adjusted for age, sex, severity of illness (APACHE III score), and baseline glomerular filtration rate;

7. Threshold changes in kidney biomarkers at 48-hours



Adjusted relative risk (aRR) estimated with multivariable Poisson regression adjusted for age, sex, severity of illness (APACHE III score), and baseline glomerular filtration rate;

6. Percentage change in kidney biomarkers at 48-hours

Outcome	VN+PT (n=42)	VN+CP (n=57)	Adjusted % change (CI_{95})[a]
Creatinine, mean (SD)			
Baseline	1.24 (0.64)	1.08 (0.46)	
48-hours	1.55 (1.16)	1.16 (1.01)	
% change	26.9 (69)	1.85 (46.4)	22.3 (-0.6, 45.1)
Cys-C, mean (SD)			
Baseline	1.23 (0.63)	1.02 (0.39)	
48-hour	1.26 (0.70)	1.08 (0.58)	
% change	8.2 (45)	11.0 (47)	-4.0 (-23.3, 15.2)

a- estimated with multivariable linear regression adjusted for age, sex, severity of illness (APACHE III score), and baseline glomerular filtration rate; VN+PT- vancomycin and piperacillin-tazobactam; VN+CP- vancomycin and cefepime; CI_{95}- 95% confidence interval

8. Conclusions

- Discordant associations between VN+PT treatment and changes of creatinine versus Cys-C suggest that associated increases in creatinine may be artifactual, related to altered tubular secretion of creatinine rather than true kidney injury
- If validated in larger study populations, our findings suggest that combined use of these two cornerstone antibiotics may not be associated with worsening kidney function in critically ill patients with sepsis.

9. References and acknowledgments

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