Comparative Incidence of Acute Kidney Injury in Septic Patients Treated with Vancomycin in Combination with Piperacillin/Tazobactam vs. Cefepime

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Background

- Empiric antibiotic therapy for patients presenting with sepsis of unknown origin is typically broad spectrum and includes coverage for *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA).
- Nephrotoxicity is a well-established adverse event of IV vancomycin and recent literature suggests that combination with piperacillin/tazobactam may increase risk for incidence of acute kidney injury (AKI) as compared to combination with other beta-lactam antibiotics.
- Some studies report patients receiving IV vancomycin and piperacillin/tazobactam are 2-3 times more likely to develop an AKI as compared to those receiving IV vancomycin and cefepime; [1,2,3] however, others report no statistically significant difference. [4,5]
- The preferred antibiotic regimen for sepsis of unknown origin at Cone Health was modified in August 2019 from IV vancomycin and piperacillin/tazobactam to IV vancomycin and cefepime.

Setting

- Cone Health is an integrated network of health care providers that includes four community hospitals located in Greensboro, Burlington, and Reidsville, NC consisting of approximately 1000 total beds.

Objectives

- The primary objective of the study was to evaluate the impact of using IV vancomycin in combination with piperacillin/tazobactam (VZ) vs. cefepime (VC) on risk of AKI in the septic population.
  - AKI was defined using RIFLE criteria, i.e. rise in SCr by 2 times baseline or decrease in GFR by 50%.[6]
- Secondary outcomes included hospital length of stay and inpatient mortality.

Methods

- Adult patients discharged with a sepsis DRG who received VZ or VC for ≥24 hours in 2012-2019 were retrospectively identified.
  - Patients were excluded for ESRD on HD, AKI occurring < 48 hours after treatment initiation or > 7 days after discontinuation, pregnancy, febrile neutropenia, or meningitis.
  - A total of 12,405 unique encounters were identified; 7,818 received VZ, 3,096 received VC, and the remainder received all three antibiotics at some time during admission.
- Collected patient information included: demographics; date of admission; comorbidities, including Charlson comorbidity index; number of doses of vancomycin; and number of doses of concomitant nephrotoxic drugs.
- Univariate comparisons were made between patients meeting RIFLE criteria for AKI and those that did not meet these criteria when receiving the same antibiotic combination.
- T-tests were used for continuous and Chi square for binary variables to determine statistically significant differences with a threshold of $p \leq 0.05$.
- Poisson models with Huber-White robust standard errors and reporting incident risk ratios were used for determining the impact of using piperacillin/tazobactam or cefepime on patient outcomes.
  - Regression models were controlled for several variables that may influence incidence of AKI.

Results

Figure 1: AKI by Drug Combination

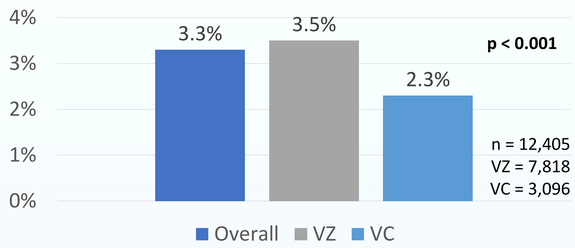


Figure 2: Proportion of AKI by Drug Combination

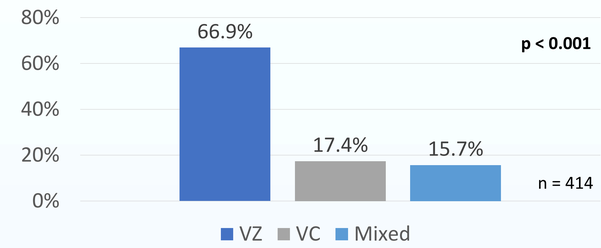


Table 1: AKI Multivariate Regression Analysis Results

	IRR*	95% CI	p value
VZ	Reference	Reference	Reference
VC	0.607	0.466 – 0.790	**< 0.001**
Age	0.981	0.974 – 0.978	**< 0.001**
Elixhauser comorbidity index	1.028	1.005 – 1.052	**0.016**
# doses of:			
Vancomycin	0.948	0.860 – 1.045	0.282
Acyclovir	0.857	0.527 – 1.394	0.535
Other antivirals	1.112	0.913 – 1.354	0.290
Antineoplastics	1.205	0.944 – 1.539	0.135
Aminoglycosides	1.033	0.578 – 1.845	0.914
Loop diuretics	1.048	1.006 – 1.092	**0.024**
ACEi/ARB	0.933	0.739 – 1.177	0.557
NSAIDs	1.080	0.958 – 1.217	0.209
Contrast media	1.092	1.004 – 1.187	**0.039**
Calcineurin inhibitors	0.447	0.185 – 1.077	0.073

*IRR: incidence rate ratio

Figure 3: Median Length of Stay in Days

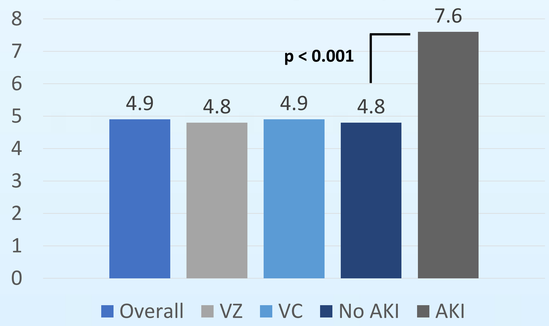


Figure 4: Inpatient Mortality

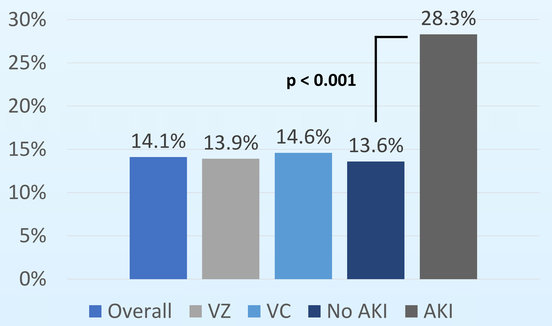
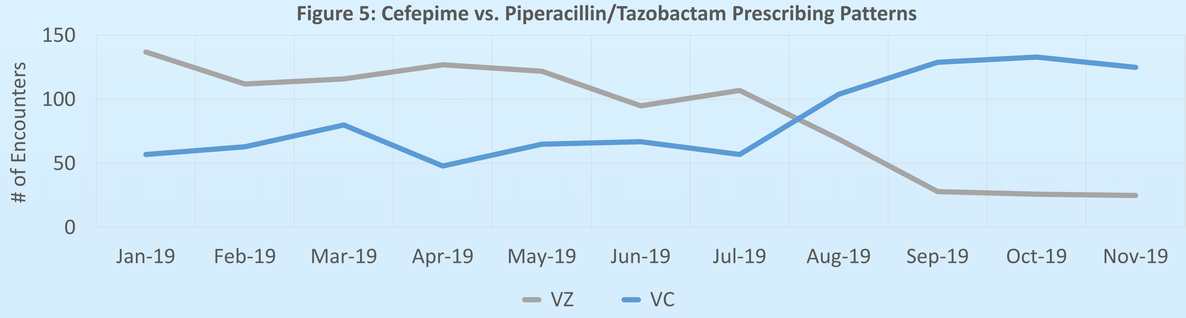


Figure 5: Cefepime vs. Piperacillin/Tazobactam Prescribing Patterns



Discussion and Conclusion

- **Incidence of AKI was significantly higher in patients who received VZ compared to those who received VC.**
  - Patients treated with VC were 40% less likely to experience an AKI compared to those treated with VZ (IRR 0.607, $p < 0.001$).
  - Patients who received either loop diuretics or contrast media were also more likely to experience an AKI.
- **There was no significant difference in hospital LOS between groups, but this may be due to a greater total number of patients in the VZ group.**
  - A higher proportion of patients receiving VZ did experience AKI but there was also a greater total number of patients not experiencing AKI, who likely had shorter hospital stays and potentially influenced the median.
  - When adjusted in the regression model, there was a statistically significant difference indicating a 4% risk reduction for an additional 1 inpatient day for patients treated with VC as compared to VZ (IRR 0.961, $p = 0.003$).
- **There was not an associated risk for inpatient mortality in the VZ group unless patients also experienced an AKI.**
  - If treated with VZ and experienced an AKI, patients were 82.3% more likely to die while hospitalized compared to patients that did not receive VZ and did not experience AKI (IRR 1.822, $p < 0.001$).
- Overall incidence of AKI was notably lower than reported in previous studies, which may be a result of including patients who received ≥24 hours of antibiotics rather than ≥48-72 hours.
- Though results were controlled for concomitant nephrotoxins and other variables that may contribute to AKI, it is not possible to control for all potential factors
  - Additionally, concomitant nephrotoxins were considered based only on the number of doses received and not weighted for differing propensity to cause AKI.
- The results of this study add to a growing body of evidence that confirms association of VZ with increased risk for AKI.
- Providers and institutions should use this information in addition to local susceptibility patterns and patient-specific risk factors to determine the most appropriate empiric antibiotic therapy to recommend for sepsis of unknown origin.

References

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Disclosures

- The authors have nothing to disclose.