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 or without parenchymal injury.

2. Methods

- 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+piperacillin (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.

3. Results

- 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.

4. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>VN+PT</th>
<th>VN+CP</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>61.5 (14.4)</td>
<td>59.4 (15.7)</td>
<td>0.138</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>139 (58)</td>
<td>164 (66)</td>
<td>0.034</td>
</tr>
<tr>
<td>Race</td>
<td>184 (63)</td>
<td>162 (67)</td>
<td>0.093</td>
</tr>
<tr>
<td>Black</td>
<td>79 (27)</td>
<td>65 (27)</td>
<td>0.000</td>
</tr>
<tr>
<td>Other</td>
<td>30 (10)</td>
<td>14 (6)</td>
<td>-0.164</td>
</tr>
<tr>
<td>Admission source, %</td>
<td>159 (66)</td>
<td>214 (73)</td>
<td>-0.154</td>
</tr>
<tr>
<td>Emergency dept.</td>
<td>60 (25)</td>
<td>52 (18)</td>
<td>0.175</td>
</tr>
<tr>
<td>Outside transfer</td>
<td>22 (9)</td>
<td>27 (9)</td>
<td>-0.003</td>
</tr>
<tr>
<td>APACHE III, mean (SD)</td>
<td>69.4 (31.6)</td>
<td>68.8 (35.3)</td>
<td>0.047</td>
</tr>
<tr>
<td>eGFR, ml/min, mean (SD)</td>
<td>76 (34)</td>
<td>63 (35)</td>
<td>-0.213</td>
</tr>
<tr>
<td>Nephrotoxins</td>
<td>1 (8)</td>
<td>38 (13)</td>
<td>-0.167</td>
</tr>
<tr>
<td>Acylcysteine</td>
<td>29 (12)</td>
<td>48 (16)</td>
<td>-0.125</td>
</tr>
</tbody>
</table>

5. Incidence of AKI and RRT at 14 days

- Count 24-hour duration initiated within 48 hours of ICU admission for severe sepsis
- Adjusted relative risk (aRR) estimated with multivariable Poisson regression adjusted for age, sex, severity of illness (APACHE III score), and baseline glomerular filtration rate; glucose;

6. Percentage change in kidney biomarkers at 48-hours

- Cystatin C, mean (SD)
  - Baseline: 1.24 (0.64) vs. 1.08 (0.46)
  - 48-hours: 1.55 (1.16) vs. 1.16 (1.01)
  - % change: 26.9 (69) vs. 1.85 (64.6)

7. Threshold changes in kidney biomarkers at 48-hours

- Cystatin C at 48 hours
  - aRR: 0.79 (CI 0.30, 0.25)

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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