Vancomycin and Piperacillin/Tazobactam Combination Therapy: The Renal Wringer?

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Pharmacy Ground Rounds
October 11th, 2016
Objectives

- Describe the mechanisms by which vancomycin and piperacillin/tazobactam could cause acute kidney injury
- Discuss current evidence regarding AKI in the setting of vancomycin and piperacillin/tazobactam combination therapy
- Identify strategies to reduce risk of AKI in patients requiring broad spectrum antibiotics
Question 1

• As a provider, I am concerned about the risk of AKI when using vancomycin and piperacillin/tazobactam combination therapy
  • A – Yes
  • B – No
Objective 1

Describe the mechanisms by which vancomycin and piperacillin/tazobactam could cause acute kidney injury
Vancomycin

- Acute tubular necrosis

Vancomycin

- Acute tubular necrosis

Vancomycin

• Associated nephrotoxicity
  • Reported in 0-5% of patients in the 1980s
  • Recent studies suggest:
    • 1% - 3.8% incidence
      • Targeting low trough levels
    • 12% - 42.6% incidence
      • Targeting high trough levels

Piperacillin/Tazobactam

• Interstitial nephritis

Piperacillin/Tazobactam

- Interstitial nephritis

Piperacillin/Tazobactam

- Interstitial nephritis

Eosinophils and Neutrophils

Inflammation

Piperacillin/Tazobactam

- Associated nephrotoxicity
  - < 1%
  - No difference between intermittent and extended infusion strategies

Vancomycin + Piperacillin/Tazobactam
Objective 2

Discuss current evidence regarding AKI in the setting of vancomycin and piperacillin/tazobactam combination therapy
Risk Factors for AKI

- Sepsis
- Critical Illness
- Nephrotoxic Drugs
- Major Surgery
- Burns
- Trauma

Risk Factors for AKI

- Dehydration/Volume Depletion
- Advanced Age
- Female
- Black Race
- CKD
- Chronic Diseases
- Diabetes Mellitus

Burgess, et al. 2014

Retrospective Cohort (n=191)

Vancomycin (n=99)  Vancomycin + Pip/Tazo (n=92)

Incidence of nephrotoxicity within 7 days of vancomycin initiation
<table>
<thead>
<tr>
<th>Description</th>
<th>Vancomycin (n=99)</th>
<th>Combination Group (n=92)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>56.3 (±15.9)</td>
<td>60.7 (±15.1)</td>
<td>-</td>
</tr>
<tr>
<td>Concomitant Nephrotoxins</td>
<td>71 (71.7%)</td>
<td>74 (80.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Vancomycin Trough Concentrations (µg/ml)</td>
<td>16.5 ± 8.2</td>
<td>17.6 ± 8.4</td>
<td>-</td>
</tr>
<tr>
<td>Sepsis</td>
<td>10 (10.1%)</td>
<td>15 (16.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>2 (2.0 %)</td>
<td>4 (4.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>1 (1.0%)</td>
<td>6 (6.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Sepsis Total</td>
<td>13 (13.1%)</td>
<td>25 (27.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>8 (8.1%)</td>
<td>15 (16.3%)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

SD = Standard Deviation

Gomes, et al. 2014

• Retrospective matched cohort (n=224)

  • Baseline SCr within 24 hours of admission
  • Treated for ≥ 48 hours
  • ≥ 1 Vancomycin trough

  Vancomycin + Pip/Tazo (n=112)

  Vancomycin + Cefepime (n=112)

Primary Outcome: Incidence of AKI
Definition: AKIN Criteria

<table>
<thead>
<tr>
<th>AKIN Criteria</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.3mg/dL or ≥ 1.5 - 2-fold from baseline</td>
<td>&lt; 0.5ml/kg/h for &gt; 6 hours</td>
<td></td>
</tr>
</tbody>
</table>

SCr = Serum Creatinine
AKIN = Acute Kidney Injury Network
AKI = Acute Kidney Injury
Pip/Tazo = Piperacillin/Tazobactam

<table>
<thead>
<tr>
<th>Description</th>
<th>Vancomycin + Cefepime (n=112)</th>
<th>Vancomycin + Pip/Tazo (n=112)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.4</td>
<td>52.4</td>
<td>0.344</td>
</tr>
<tr>
<td>Male</td>
<td>57.1%</td>
<td>58.9%</td>
<td>0.787</td>
</tr>
<tr>
<td>Weight</td>
<td>83.2 kg</td>
<td>91.5 kg</td>
<td>0.004</td>
</tr>
<tr>
<td>SCr at antibiotic start</td>
<td>0.74 mg/dl</td>
<td>0.79 mg/dl</td>
<td>0.413</td>
</tr>
<tr>
<td>ICU during admission</td>
<td>64.3%</td>
<td>46.4%</td>
<td>0.009</td>
</tr>
<tr>
<td>Contrast</td>
<td>45.5%</td>
<td>42.0%</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>22.3%</td>
<td>38.4%</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean days of antibiotic therapy</td>
<td>6.7</td>
<td>7.1</td>
<td>0.003</td>
</tr>
<tr>
<td>AKI incidence</td>
<td>12.5%</td>
<td>34.8%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SCr = Serum Creatinine
Pip/Tazo = Piperacillin/Tazobactam
AKI = Acute Kidney Injury

## Gomes, et al. 2014

<table>
<thead>
<tr>
<th>Description</th>
<th>Vancomycin + Cefepime (n=55)</th>
<th>Vancomycin + Pip/Tazo (n=55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.1</td>
<td>51.4</td>
<td>0.875</td>
</tr>
<tr>
<td>Male</td>
<td>47.3%</td>
<td>43.6%</td>
<td>0.834</td>
</tr>
<tr>
<td>Weight</td>
<td>85.8 kg</td>
<td>89.1 kg</td>
<td>0.467</td>
</tr>
<tr>
<td>SCr at antibiotic start</td>
<td>0.74 mg/dl</td>
<td>0.75 mg/dl</td>
<td>0.776</td>
</tr>
<tr>
<td>ICU during admission</td>
<td>52.7%</td>
<td>52.7%</td>
<td>1.000</td>
</tr>
<tr>
<td>Contrast</td>
<td>32.7%</td>
<td>34.6%</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>30.9%</td>
<td>32.7%</td>
<td>1.000</td>
</tr>
<tr>
<td>Mean days of antibiotic therapy</td>
<td>Not provided</td>
<td>Not provided</td>
<td>-</td>
</tr>
<tr>
<td>AKI incidence</td>
<td>10.9%</td>
<td>36.4%</td>
<td>&lt; 0.003</td>
</tr>
</tbody>
</table>

SCr = Serum Creatinine  
Pip/Tazo = Piperacillin/Tazobactam  
AKI = Acute Kidney Injury
Gomes, et al. 2014

**Limitations**

- Single Center
- Severity of Illness Score
- AKI type
- Sepsis

**Conclusion:** Results suggest ↑ risk

- Unknown variables ↓ confidence
Moenster, et al. 2013
Diabetics with osteomyelitis
Vancomycin + Pip/Tazo (n=109)
Vancomycin + Cefepime (n=30)

ICU
Vancomycin + Pip/Tazo (n=49)
Vancomycin + Cefepime (n=73)

AKI = Acute Kidney Injury
Pip/Tazo = Piperacillin/Tazobactam
ICU = Intensive Care Unit

Incidence of AKI

Hammond

- Vancomycin + Pip/Tazo: 32.7%
- Vancomycin + Cefepime: 28.8%

P = 0.761

Moenster

- Vancomycin + Pip/Tazo: 29.3%
- Vancomycin + Cefepime: 13.3%

P = 0.09

AKI = Acute Kidney Injury
Pip/Tazo = Piperacillin/Tazobactam


- Prospective Cohort (n=85)

Pip/Tazo, cefepime, or meropenem ≥ 72 hours with steady state vancomycin trough

Vancomycin + Pip/Tazo (n=59)

Vancomycin + Cefepime or Meropenem (n=26)

Primary Outcome: Development of AKI
Definition: AKIN Criteria

Exclusion Criteria

<table>
<thead>
<tr>
<th>Renal replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SCr &gt; 2.5 mg/dL</td>
</tr>
</tbody>
</table>

SCr = Serum Creatinine
AKI = Acute Kidney Injury
Pip/Tazo = Piperacillin/Tazobactam

**Peyko, et al. 2016**

<table>
<thead>
<tr>
<th>Description</th>
<th>Vancomycin + Cefepime or Meropenem (n=26)</th>
<th>Vancomycin + Pip/Tazo (n=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>34.6%</td>
<td>47.5%</td>
<td>0.271</td>
</tr>
<tr>
<td>UTI</td>
<td>15.4%</td>
<td>3.4%</td>
<td>0.047</td>
</tr>
<tr>
<td>IAI</td>
<td>7.7%</td>
<td>0%</td>
<td>0.031</td>
</tr>
<tr>
<td>Sepsis of unknown origin/bacteremia</td>
<td>3.9%</td>
<td>10.2%</td>
<td>0.328</td>
</tr>
<tr>
<td>SSTI</td>
<td>19.2%</td>
<td>20.3%</td>
<td>0.906</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>3.9%</td>
<td>11.9%</td>
<td>0.243</td>
</tr>
<tr>
<td>Other</td>
<td>15.4%</td>
<td>6.8%</td>
<td>-</td>
</tr>
</tbody>
</table>

UTI = Urinary Tract Infection  
IAI = Intra-abdominal Infection  
SSTI = Skin and Soft Tissue Infection
<table>
<thead>
<tr>
<th>Description</th>
<th>Vancomycin + Cefepime or Meropenem (n=26)</th>
<th>Vancomycin + Pip/Tazo (n=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>74</td>
<td>74.8</td>
<td>0.814</td>
</tr>
<tr>
<td>Male</td>
<td>57.7%</td>
<td>44.1%</td>
<td>0.701</td>
</tr>
<tr>
<td>Baseline SCr</td>
<td>1.2 mg/dl</td>
<td>1.0 mg/dl</td>
<td>0.193</td>
</tr>
<tr>
<td>Nephrotoxic agents</td>
<td>38.5%</td>
<td>33.9%</td>
<td>0.685</td>
</tr>
<tr>
<td>Vasopressor</td>
<td>15.4%</td>
<td>13.6%</td>
<td>0.823</td>
</tr>
<tr>
<td>Diabetic</td>
<td>50%</td>
<td>32.2%</td>
<td>0.118</td>
</tr>
<tr>
<td>CKD at baseline</td>
<td>19.2%</td>
<td>20.3%</td>
<td>0.906</td>
</tr>
<tr>
<td>Vancomycin troughs</td>
<td>18.3 µg/mL</td>
<td>16.6 µg/mL</td>
<td>0.331</td>
</tr>
<tr>
<td>Development of AKI</td>
<td>7.7%</td>
<td>37.3%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

SCr = Serum Creatinine  
CKD = Chronic Kidney Disease  
Pip/Tazo = Piperacillin/Tazobactam  
AKI = Acute Kidney Injury  


Limitations

- Single Center
- AKI type
- Degree of Sepsis
- Small sample size
- Antibiotic Selection

• Conclusion: Results suggest ↑ risk
  • Small sample size and unknown variables ↓ confidence

AKI = Acute Kidney Injury
So where does this leave us?
Objective 3

Identify strategies to reduce risk of AKI in patients requiring broad spectrum antibiotics
Risk Reduction Strategies

- Minimize Vasopressors
- Minimize High Dose Diuretics
- Minimize NSAIDS

NSAIDS = Non-Steroidal Anti-Inflammatory Drugs

Risk Reduction Strategies

- Continually Reassess
- Antibiotics Indicated?
- Deescalation
Risk Factors for AKI

- Vancomycin
  - High-dose regimens
    - > 4g/day
  - High trough serum level
  - Duration of therapy
    - > 1 week incidence 6-21%
    - > 2 weeks incidence up to 30%

Risk Reduction Strategies

- Target lower trough goals when possible
- Minimize doses >4g per day

Minimize Vancomycin Exposure

Question 2

What is the proposed mechanism for vancomycin-associated nephrotoxicity?

A – Acute Glomerulonephritis
B – Acute Interstitial Nephritis
C – Acute Tubular Necrosis
Question 3

• Which of the following is not a risk factor for AKI?
  • A – Sepsis
  • B – Male gender
  • C – Critical illness
  • D – Advanced Age
Question 4

• Which of the following is an appropriate intervention to decrease risk of AKI in the setting of vancomycin + pip/tazo combination therapy?
  • A – Avoiding high dose diuretics
  • B – Deescalation following cultures and sensitivities
  • C – Utilizing lower vancomycin trough goals
  • D – All of the above
Question 5

• As a provider, I am concerned about the risk of AKI when using vancomycin and piperacillin/tazobactam combination therapy
  • A – Yes
  • B – No
Summary

• The mechanism by which the combination of vancomycin and pip/tazo may cause AKI is currently unknown

• Studies are inconclusive regarding increased risk of AKI with combination therapy

• The risk of AKI can be reduced by avoiding nephrotoxic medications, continually reassessing antibiotic therapy, and limiting vancomycin exposure
Questions & Discussion

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