Vancomycin plus Piperacillin/Tazobactam….Bad for the Beans?

Emmanuel U. Aniemeke, Pharm.D.
PGY1 Pharmacy Resident
University Health System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas Health Science College of Pharmacy
Pharmacotherapy Education and Research Center
The University of Texas Health Science Center San Antonio

Pharmacotherapy Rounds
February 27th, 2015

LEARNING OBJECTIVES
1. Describe the pathophysiology, clinical presentation, and causes of acute kidney injury
2. Summarize the proposed mechanism of acute kidney injury associated with vancomycin and piperacillin/tazobactam
3. Evaluate the current literature regarding the risk of acute kidney injury while on combination vancomycin and piperacillin/tazobactam therapy
4. Provide practical recommendations regarding the combined use of vancomycin and piperacillin/tazobactam based on recently published literature
ACUTE KIDNEY INJURY (AKI)

I. **BACKGROUND** ¹, ², ³
   A. Sudden (hours to days) decline in excretory function of the kidney
   B. Characterized by
      i. Dysregulation of fluids, electrolytes and acid-base balance
      ii. Decreased glomerular filtration rate (GFR)
      iii. Increase in serum creatinine ($S_c$)

II. **EPIDEMIOLOGY/INCIDENCE** ¹, ², ⁴
   A. Associated with significantly high mortality and morbidity rates
   B. Incidence
      i. Community-acquired: <1%
      ii. Hospital-acquired: ~9%
      iii. ICU-acquired: 30-67%

III. **ETIOLOGY** ¹, ⁵, ⁶, ⁷

![Figure 1: Pathophysiology of AKI]⁵

¹, ², ³, ⁴, ⁵, ⁶, ⁷ Refer to specific sources or literature for detailed information.
### Table 1: CLASSIFICATION, PATHPHYSIOLOGY AND CAUSES OF AKI

<table>
<thead>
<tr>
<th>Classifications</th>
<th>Pathophysiology</th>
<th>Common causes</th>
<th>Associated medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRERENAL (25-60%)</td>
<td>Decreased renal perfusion</td>
<td>Volume depletion Heptorenal syndrome Systemic vasodilation</td>
<td>NSAIDs Cyclosorine RAAS inhibitors Tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTRINSIC (35-70%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute tubular necrosis (ATN)</td>
<td>Ischemic or toxic tubular damage</td>
<td>Ischemic insults Nephrotoxic agents</td>
<td>Vancomycin Aminoglycosides Methotrexate Amphotericin B</td>
</tr>
<tr>
<td>Acute interstitial nephritis (AIN)</td>
<td>Interstitial damage</td>
<td>Infections Sarcoidosis Lupus</td>
<td>Penicillin analogues Cephalosporins Sulfonamides Ciprofloxacin Acyclovir Rifampin Proton pump inhibitors NSAIDs</td>
</tr>
<tr>
<td>POSTRENAL (&lt;5%)</td>
<td>Urinary Obstruction</td>
<td>Prostate hypertrophy Neurogenic bladder</td>
<td>Acyclovir Indinavir</td>
</tr>
</tbody>
</table>

NSAIDs, Non-steroidal anti-inflammatory drugs; RAAS, rennin-angiotensin-aldosterone system

### IV. DEFINITION AND STAGING

### Table 2: AKI STAGING

<table>
<thead>
<tr>
<th>RIFLE CRITERIA</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIFLE Category</strong></td>
<td><strong>GFR Criteria</strong></td>
<td><strong>UO Criteria</strong></td>
</tr>
<tr>
<td>Risk</td>
<td>1.5-fold increase in (S_{cr}) or GFR decrease &gt; 25%</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 6 \text{ h})</td>
</tr>
<tr>
<td>Injury</td>
<td>2-fold increase in (S_{cr}) or GFR decrease &gt; 50%</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 12 \text{ h})</td>
</tr>
<tr>
<td>Failure</td>
<td>3-fold increase in (S_{cr}) or GFR decrease &gt; 75% or (S_{cr} \geq 4 \text{ mg/dL, or acute rise in } S_{cr} \geq 0.5 \text{ mg/dL})</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 24 \text{ h or anuria for } \geq 12 \text{ h})</td>
</tr>
<tr>
<td>Loss</td>
<td>Complete loss of kidney function &gt; 4 weeks</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage kidney disease (&gt;3 months)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AKIN CRITERIA</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AKIN Stage</strong></td>
<td><strong>S_{cr} Criteria</strong></td>
<td><strong>UO Criteria</strong></td>
</tr>
<tr>
<td>1</td>
<td>Increase in (S_{cr}) to (\geq 0.3 \text{ mg/dL or 1.5- to 2-fold from baseline})</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 6 \text{ h})</td>
</tr>
<tr>
<td>2</td>
<td>Increase in (S_{cr}) to &gt; 2-to 3-fold from baseline</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 12 \text{ h})</td>
</tr>
<tr>
<td>3</td>
<td>Increase in (S_{cr}) to &gt; 3-fold from baseline or (\geq 4 \text{ mg/dL (\geq 354 } \mu \text{mol/L) with an acute increase of at least 0.5 mg/dL or on RRT})</td>
<td>(UO &lt; 0.3 \text{ mL/kg/h for } \geq 24 \text{ h or anuria for } \geq 12 \text{ h})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>K-DIGO CRITERIA</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>K-DIGO Stage</strong></td>
<td><strong>S_{cr} Criteria</strong></td>
<td><strong>UO Criteria</strong></td>
</tr>
<tr>
<td>1</td>
<td>Increase in (S_{cr}) to (\geq 0.3 \text{ mg/dL or 1.5- to 1.9 times from baseline})</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 6 \text{ h})</td>
</tr>
<tr>
<td>2</td>
<td>Increase in (S_{cr}) 2 to 3 times from baseline</td>
<td>(UO &lt; 0.5 \text{ mL/kg/h for } \geq 12 \text{ h})</td>
</tr>
<tr>
<td>3</td>
<td>Increase in (S_{cr}) 3 times from baseline or (\geq 4 \text{ mg/dL (\geq 354 } \mu \text{mol/L) or initiation of renal replacement therapy or in patients } &lt; 18 \text{ years, decrease in eGFR to } &lt; 35 \text{ mL/min per } 1.73 \text{m}^2)</td>
<td>(UO &lt; 0.3 \text{ mL/kg/h for } \geq 24 \text{ h or anuria for } \geq 12 \text{ h})</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; \(S_{cr}\), Serum creatinine; OU, Urine output; RRT, Renal replacement therapy; AKIN, Acute Kidney Injury Network; K-DIGO, Kidney Disease Improvement Global Outcomes
I. **BACKGROUND** 8, 9, 10
   A. Vancomycin
      i. Glycopeptide antibiotic
      ii. Early formulation of vancomycin contained significant impurities, nicknamed “Mississippi mud”
      iii. Subsequent formulations increased the purity, reducing the severities of toxicity
      iv. Cornerstone antibiotic for management of severe gram-positive infections
         1. Methicillin-resistant *Staphylococcus aureus* (MRSA)
         2. Methicillin-resistant coagulase-negative staphylococci
         3. Non-vancomycin-resistant enterococci
   B. Primary renal excretion
      i. Glomerular filtration and active tubular secretion (90%)
      ii. Hepatic conjugation (~10%)

II. **MECHANISM OF ACTION** 8
    A. Inhibits cell wall synthesis of gram-positive bacteria
    B. Inhibition of peptidoglycan elongation and cross-linking
    C. Slowly bactericidal

V. **ADVERSE EFFECTS** 8, 11, 12
   A. Nephrotoxicity (5-43%)
   B. Infusion reactions: “Redman syndrome”
   C. Drug fever
   D. IgA bullous dermatosis

VI. **POSTULATED MECHANISM OF VAN** 8, 13, 14, 15, 16, 17
   A. Drug-induced oxidative stress
   B. Mitochondrial damage in the proximal renal tubular cell
   C. Proximal renal tubular cell necrosis
   D. Contribution to complement pathway and inflammation
   E. Believed to be mostly reversible
VII. **INCIDENCE OF VAN**\(^9, 13, 14, 15, 16, 17\)

A. Incidence ranges from 5 - 43 %

B. Associated with
   i. Prolonged hospitalization
   ii. Increased mortality
   iii. Need for renal replacement therapy

VIII. **EVIDENCE OF VAN**

<table>
<thead>
<tr>
<th>Author &amp; Study Design</th>
<th>Patient Characteristics</th>
<th>Treatment Groups</th>
<th>VAN Outcome</th>
<th>Risk Factor</th>
</tr>
</thead>
</table>
| Hidayat et al., 2006\(^9\) (Prospective study) | Adult patients with hospital-acquired infections (MRSA) n=95 | Low trough (< 15mg/L) vs. High trough (> 15mg/L) | • High trough: 12%  
• Low trough: None | • High trough |
| Lodise et al., 2008\(^10\) (Retrospective study) | Adult patients with suspected or proven gram-positive infection n=291; VM=246, Linezolid=45 | Standard VM dose (< 4g/day), High VM dose (> 4g/day) and Linezolid for > 48 hours | • High doses: 34.6%  
• Standard dose 10.9%  
• Linezolid: 6.7% | • High VM dose  
• Concomitant nephrotoxic agents  
• Septic shock |
| Lodise et al., 2009\(^21\) (Retrospective study) | Adults patients with suspected or proven gram-positive infection n=166; High dose=27, Std dose=139 | VM for > 48 hours, with ≥ 1 VM trough level collected within 96 hours of therapy | • 12.7% | • High initial trough |
| Bosso et al., 2011\(^22\) (Prospective study) | Adult patients with MRSA infections n=288 | Low vs. high trough, (< 15mg/L vs. > 15mg/L) | • High trough group: 29.6%  
• Low trough: 8.9% | • High troughs  
• Race (black) |
| Minejima et al., 2011\(^23\) (Prospective study) | Elderly patients (median, 70 years), with invasive infections n=227 | Loading dose, maintenance dose | • 19%  
• High trough group: 24%  
• Low trough: 17% | • ICU stay  
• Low baseline GFR  
• Malignancy  
• Prior episode of AKI |
| Cano et al., 2012\(^24\) (Retrospective study) | Adult ICU pneumonia patients n=188 | At least one dose of VM, and trough levels were monitored | • 15.4% | • Duration of exposure  
• Aminoglycoside use |
| Prabaker et al., 2012\(^25\) (Retrospective study) | Adult patients with various infections n=348 | ≥ 5 days of VM therapy | • Overall: 8.9% | • Contrast dye  
• Higher trough |
| Wunderink et al., 2012\(^26\) (Prospective study) | Adult patients with MRSA nosocomial pneumonia n=448; VM=172, Linezolid=176 | Linezolid 600 mg q 12 h VM 15mg/kg q 12 h | • VM (18.2%)  
• Linezolid (8.4%) | • VM exposure  
• Higher trough |

AKI, Acute kidney injury; VAN, vancomycin associated nephrotoxicity; VM, vancomycin; ICU, intensive care unit; Std, standard
IX. **RISK FACTORS**

<table>
<thead>
<tr>
<th>Table 6: RISK FACTOR FOR VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
</tbody>
</table>
| Vancomycin exposure-related factors | • Larger vancomycin exposures  
  o Higher Troughs > 15 mg/L  
  o Increased exposure (increased area under the curve)  
  o Prolonged durations |
| Host-related factors        | • History of acute kidney injury  
  • Pre-existing renal insufficiency  
  • Critically ill  
  • Septic |
| Concurrent nephrotoxins     | • Loop diuretics  
  • Acyclovir  
  • Amphotericin B  
  • Aminoglycosides  
  • Contrast dye |
| Other factors               | • Disease-state specific nephrotoxicity  
  • Obesity  
  • African-American race  
  • Treatment of complicated infections (HCAP, osteomyelitis, meningitis, endocarditis, and bacteremia) |

**PENICILLIN ASSOCIATED NEPHROTOXICITY**

I. **BACKGROUND**

A. Penicillin
   i. Oldest available pure antibiotic
   ii. Isolated by Sir Alexander Fleming in 1928, from fungi, *Penicillium notatum*
   iii. Primarily eliminated renally ~ 60-90%
      a. 10% glomerular filtration
      b. 90% tubular secretion

II. **MECHANISM OF ACTION**

A. Inhibits cell wall synthesis
B. Binds irreversibly to the penicillin-binding-proteins
C. Inhibition of peptidoglycan elongation and cross-linking
D. Rapid bactericidal time-dependent killing

III. **ADVERSE EFFECTS**

A. Acute interstitial nephritis
B. Gastrointestinal upset
C. Hypersensitivity reactions
IV. POSTULATED MECHANISM OF NEPHROTOXICITY \(^{29, 30, 31, 32}\)
A. Dimethoxyphenylpenicilloyl (DPO) binding to host renal structural protein
B. Formation an antigen-protein complex (hapten) along the tubular basement membrane
C. Mounting an immunogenic response developing into interstitial nephritis

V. PIPERACILLIN-TAZOBACTAM (PT) \(^{33, 34, 35}\)
A. Extended-spectrum semisynthetic penicillin combined with ß-lactamase inhibitor
B. Approved by the FDA in 1993
C. Composed at an 8:1 ratio of piperacillin and tazobactam
D. FDA Indications
   i. Nosocomial pneumonia
   ii. Intra-abdominal infections
   iii. Skin and soft tissue infections
   iv. Pelvic inflammatory disease
   v. Septicemia
   vi. Neutropenic fever
   vii. Osteomyelitis
   viii. Septic arthritis

VI. EVIDENCE OF PIPERACILLIN-TAZOBACTAM ASSOCIATED NEPHROTOXICITY

<table>
<thead>
<tr>
<th>Author &amp; Study design</th>
<th>Patient Characteristics</th>
<th>Regimen</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pill et al., 1997(^{36})</td>
<td>51-year old woman with acute leukemia</td>
<td>PT, allopurinol, and VM</td>
<td>6 days of PT + 7 days of VM/ allopurinol</td>
<td>AIN caused by PT</td>
</tr>
<tr>
<td>(Case report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanaka et al., 1997(^{38})</td>
<td>11-year old with suspicion of renal disease</td>
<td>PT</td>
<td>4 days of PT treatment</td>
<td>PT confirmed as causative agent by positive laboratory and renal biopsy findings</td>
</tr>
<tr>
<td>(Case report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sakarcan et al., 2001(^{29})</td>
<td>13-year old with cystic fibrosis</td>
<td>PT, levofloxacin, cefuroxime</td>
<td>Two separate PT treatments, 5 years apart</td>
<td>PT identified as the culprit of AIN</td>
</tr>
<tr>
<td>(Case report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polderman et al., 2002(^{39})</td>
<td>73 adult patients PT group = 43, Control group = 40</td>
<td>PT vs. Control (cephalosporins or ciprofloxacin)</td>
<td>36 hours of PT or control</td>
<td>PT may cause or aggravate electrolyte disorders and tubular dysfunction in ICU patients when (S_c) levels remain normal</td>
</tr>
<tr>
<td>(Prospective, observational)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al., 2012(^{37})</td>
<td>56-year old man with osteomyelitis</td>
<td>PT</td>
<td>6 weeks of PT</td>
<td>PT can result in drug induced AIN</td>
</tr>
<tr>
<td>(Case report)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

VM, vancomycin; PT, piperacillin/tazobactam; AIN, acute interstitial nephritis; ICU, intensive care unit; \(S_c\), serum creatinine
I. CLINICAL QUESTION
A. Does the combination therapy of vancomycin and piperacillin/tazobactam (VPT) increase the risk incidence of nephrotoxicity?

II. ABSTRACT EVALUATION
A. Hellwig et al. ⁴⁰
i. Retrospective evaluation of 735 adult patients over a 6 month period
ii. Compared patients who received VM alone versus PT alone versus combination therapy of VPT for more than 48 hours
iii. AKI defined as increase of serum creatinine greater than 0.5 mg/dL or a 50% increase from baseline
iv. Result

<table>
<thead>
<tr>
<th>Table 8: INCIDENCE OF AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
</tr>
<tr>
<td>General medicine</td>
</tr>
<tr>
<td>ICU</td>
</tr>
</tbody>
</table>

VM, vancomycin; PT, piperacillin/tazobactam; VPT, vancomycin and piperacillin/tazobactam

B. Min et al. ⁴¹
i. Evaluation of 140 surgical ICU patients over one year
ii. Compared patients on the combination therapy of VPT versus monotherapy of VM alone for at least 48 hours
iii. AKI defined as increase of serum creatinine more than 1.5 times baseline during antibiotic therapy
iv. Result
- Incidence of AKI
  - VPT group (40.5%)
  - VM group (9.0%)
  - p<0.001

III. LITERATURE REVIEW
A. Meaney et al. Pharmacotherapy 2014
B. Burgess et al. Pharmacotherapy 2014
D. Gomes et al. Pharmacotherapy 2014

Aniemeke 8

**Objective**
- To determine the incidence, time-course, outcomes, and risk factors of VM among adult internal medicine patients

**Design**
- Single-center, retrospective cohort study, (January 1, 2009-December 31, 2009)

**Population**
- **Inclusion**
  - Men or women ≥ 18 years
  - Admitted to an internal medicine service, treated with VM for ≥72 hours
- **Exclusion**
  - Patients diagnosed with AKI or chronic kidney disease (CKD)
  - Initial $S_{cr} ≥ 1.4$ mg/dL for women and ≥1.5 mg/dL for men
  - Diagnosis of kidney injury due to causes other than VM therapy

**Outcomes**
- **Endpoints**
  - Incidence of nephrotoxicity: Increase in $S_{cr}$ by 0.5 mg/dL or 50% above baseline
  - The outcome of the nephrotoxicity event, described as either return to $S_{cr}$ to baseline (defined as within 20% of the baseline value), development of CKD or dialysis dependence

**Statistical Analysis**
- Chi-square test or fisher exact test for categorical variables analysis
- Student t-test for continuous, normally distributed data
- Wilcoxon Rank Sum test for non-normal continuous data and ordinal data
- Multiple regression analysis for bivariate assessment resulted in p value <0.20
- Covariates identified as potential confounders and non significant covariates were included in the regression models

**Results**
- n=125 adult patients; Nephrotoxicity group (n=17), No nephrotoxicity group (n=108)
- Age (mean): 50.9 ± 15.5

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nephrotoxicity (n=17)</th>
<th>No nephrotoxicity (n=108)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1</td>
<td>26</td>
<td>0.049</td>
</tr>
<tr>
<td>Baseline CrCl (ml/min) mean</td>
<td>91.5 ± 26.7</td>
<td>83.5 ±27.7</td>
<td>0.267</td>
</tr>
<tr>
<td>VM daily dose (mg/kg)</td>
<td>29.3 ± 9.5</td>
<td>26.2 ± 7.4</td>
<td>0.1291</td>
</tr>
<tr>
<td>Daily dose &gt;4g, n (%)</td>
<td>2 (11.8)</td>
<td>4 (3.7)</td>
<td>0.188</td>
</tr>
<tr>
<td>Trough ≥ 15mg/L, n (%)</td>
<td>6 (46.20)</td>
<td>28 (32.6)</td>
<td>0.360</td>
</tr>
<tr>
<td>Hypotensive event, n (%)</td>
<td>3 (17.7)</td>
<td>1 (0.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Eosinophilia, n (%)</td>
<td>5 (29.4)</td>
<td>1 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin/Skin Structure Infection, n (%)</td>
<td>5 (29.4)</td>
<td>51(47.2)</td>
<td>0.170</td>
</tr>
<tr>
<td>PT treatment, n (%)</td>
<td>13 (76.5)</td>
<td>45 (41.7)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

- Cumulative incidence of VAN: 13.6% (17/125)
- Nephrotoxicity developed at a median of 4.5 days (IQR: 2.2-4.9) and peaked at 5.7 days (IQR: 3.8-9.6)
- Acute hypotensive events, creatinine clearance, Charlson Comorbidity index (refer to appendix 1), and use of PT were associated with VAN
- PT was associated with 5.36-fold increased odds of VAN (95% CI 1.41-20.5) after controlling for acute hypotensive events, creatinine clearance, Charlson Comorbidity index
- Concomitant nephrotoxic drugs included; ACEI, allopurinol, acyclovir, aminoglycoside, amphotericin, ganciclovir, IV contrast agent, loop diuretic, NSAID, TMP-SMX, tenofovir, and beta-lactams

**Strengths**
- Focused on one level of patient care (internal medicine patients), hence reducing confounding variables
### Limitations

- Retrospective, unblinded
- Small sample size within the nephrotoxic group, hence limited data on significant differences in occurrence of the risk factors between groups
- Large type II error on variable analysis
- Stability of $S_c$ was not assessed before the patient were entered into the study
- Wide confidence intervals, low precision
- Exclusion of treatment related variables, such as dose, trough concentrations, patient weight ≥ 101.4kg or 2 or more concomitant nephrotoxic agents in the regression model

### Authors Conclusion

- Use of concomitant piperacillin-tazobactam is significantly associated with development of nephrotoxicity

### Take Home Points

- Higher acuity patients are at risk for VAN
- Nephrotoxicity was seen after 4 days of therapy
- AKI developed from VPT is reversible

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**Burgess LD, Drew RH. Comparison of the incidence of VAN in hospitalized patients with and without concomitant piperacillin-tazobactam. Pharmacotherapy. 2014; 34(7):670-6.**

**Objective**

- To determine whether the addition of piperacillin-tazobactam leads to an increased incidence of nephrotoxicity in patients receiving VM
- To explore potential confounding factors that may increase the risk of VAN

**Design**

- Single-center, retrospective cohort study (July 1, 2009-July 1, 2012)

**Population**

**Inclusion**

- Men or women ≥ 18 years, who received a minimum of 48 hours of IV VM with or without PT for any indication
- Patients with four $S_c$ values measured on four separate days during admission

**Exclusion**

- Patients with underlying renal dysfunction, defined as:
  - $S_c$ > 1.5 mg/dL or a creatinine clearance (CrCl) of < 30 mL/min based on the Cockcroft-Gault equation
  - Any previous history of renal replacement therapy
  - Recent history of AKI: 1.5-fold increase in $S_c$ from baseline and before the initiation of VM

**Outcomes**

**Primary endpoint**

- Incidence of nephrotoxicity: defined as a minimum 1.5-fold increase in the patient’s $S_c$ based on the maximum measured $S_c$ value within the first 7 days of VM treatment from the $S_c$ measured within 48 hours before initiating VM

**Secondary endpoints**

- Incidence of nephrotoxicity in adult hospitalized patients receiving VM intravenous therapy with and without the following risk factors:
  - Any use of concomitant nephrotoxic agents
  - Advanced age
  - A measured or estimated steady-state VM trough concentration of 15 μg/ml or greater
  - Elevated Charlson Comorbidity Index, or a total VM dosage of 4 g/day or greater in the first 7 days of therapy

**Statistical Analysis**

- $n=180$ patients per group required to achieve a statistical power of 80% to detect a 15% difference between the VPT group (25%) and VM group (10%)
- Chi-square test for the association of the addition of PT to the incidence of nephrotoxicity
- Univariate logistic regression analysis for the main exposure variable of PT addition and potential risk factors for nephrotoxicity
- Multivariate logistic regression model to assess the association of nephrotoxicity with addition of PT
Results

Table 10: Demographic and Clinical Characteristics by Treatment Group

<table>
<thead>
<tr>
<th>Description</th>
<th>VM (n=99)</th>
<th>VPT (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males n (%)</td>
<td>48 (48.5)</td>
<td>54 (56.7)</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>56.3± 15.9</td>
<td>60.7± 15.1</td>
</tr>
<tr>
<td>Concomitant nephrotoxins n (%)</td>
<td>71 (71.7)</td>
<td>74 (80.4)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ICU admission n (%)</td>
<td>19 (19.2)</td>
<td>14 (15.2)</td>
</tr>
<tr>
<td>Sepsis: VM group n (%)</td>
<td>10 (10.1)</td>
<td>15 (16.3)</td>
</tr>
<tr>
<td>Severe sepsis n (%)</td>
<td>2 (2.0)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Septic shock n (%)</td>
<td>1 (1.0)</td>
<td>6 (6.5)</td>
</tr>
</tbody>
</table>

Outcome Analysis

Table 11: OUTCOME ANALYSIS OF TREATMENT GROUP

<table>
<thead>
<tr>
<th>Description</th>
<th>VM (n=99)</th>
<th>VPT (n=92)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of nephrotoxicity (%)</td>
<td>8 (8.0)</td>
<td>15 (16.3)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Secondary Endpoint (Univariate analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (OR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.95-1.01</td>
</tr>
<tr>
<td>Concomitant nephrotoxic agents</td>
<td>1.16</td>
<td>0.41-3.33</td>
</tr>
<tr>
<td>VM trough concentrations ≥15μg/mL</td>
<td>3.67</td>
<td>1.49-9.03</td>
</tr>
</tbody>
</table>

- The multivariate analysis of VPT resulted in an OR of 2.48 ( p=0.032, CI >1.11); one-sided T-test
- VM troughs (mean) were similar between groups and no patient in either group received 4g/day or more of VM
- Only measured or estimated trough concentration of ≥15mg/L was associated with an increased risk of nephrotoxicity

Strengths

- Large study
- Stability of Scr was assessed before the patient were entered into the study
- Inclusion of patients with stable renal function in the study at baseline minimize the impact of treatment duration being a confounder

Limitations

- Retrospective, unblinded
- Duration of exposure of patient to nephrotoxic agents or comorbid conditions were not stated
- Notable differences between groups in the incidence of sepsis
- Data on the number of patients receiving which specific other nephrotoxic agents not provided

Authors Conclusion

- Patients receiving VPT therapy have a significantly increased risk of developing nephrotoxicity

Take Home Points

- Trough concentrations ≥15mg/L increased incidence of nephrotoxicity
- Power analysis is flawed because it is based on unproven data
- Significant difference in treatment groups (i.e., severe sepsis, septic shock)
- Severity of illness increases risk of AKI


Objective

- To compare the potential rate of AKI between VPT and VC

Design

- Single-center, retrospective cohort study (January 1, 2006 – December 31, 2011)

Inclusion

- Diagnosis of diabetes
- Diagnosis of osteomyelitis with determination to treat by an infectious disease physician
- Treatment with either VPT or VC for at least 72h

Exclusion

- Baseline CrCl ≤ 40 mL/min
- Baseline blood urea nitrogen (BUN)/Scr ratio ≥20:1, or absolute neutrophil count <500 cells/mm³
- Recipient of IV acyclovir, amphotericin B, any aminoglycoside or any vasopressor concurrently or within 48 h of antibiotic initiation

Outcomes

- Rate of AKI: Increase in baseline Scr of 50% or 0.5mg/dL between the two groups of patients
  - Patients were stratified into high-dose (≥3 g of cefepime per 24 h, or ≥ 18 g of PT per 24 h) or non-high-dose
therapy

Statistical Analysis
- n = 200 patients per group was required to achieve a statistical power of 80%, to detect a 19% difference between groups
- Chi-square test or Fisher’s exact test to compare non-parametric data
- Student’s t-test to evaluate parametric data, an alpha of <0.05 was considered significant

Results
- n = 139: VPT = 109, VC = 30
  - High dose therapy: VPT = 32, VC = 17

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VPT (n=109)</th>
<th>VC (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.8</td>
<td>58.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Haemoglobin A1c</td>
<td>6.6</td>
<td>4.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Loop diuretics, n (%)</td>
<td>25 (22.9)</td>
<td>14 (46.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Contrast dye, n (%)</td>
<td>14 (12.8)</td>
<td>3 (10)</td>
<td>0.036</td>
</tr>
<tr>
<td>Average CrCl at initiation (ml/min)</td>
<td>72</td>
<td>80.02</td>
<td>0.06</td>
</tr>
<tr>
<td>High-dose therapy recipient, n (%)</td>
<td>24 (22)</td>
<td>17 (56.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Outcome Analysis
- 25.9% (36/139) of all patients developed AKI
  - High dose therapy: AKI: 33% (12/36), no AKI: 28.1% (29/103)
- No statistical differences between average total duration, average VM troughs or use nephrotoxic agents (loop diuretics, ACEI or contrast dye) between patients who developed AKI and those who did not

Strengths
- Homogeneity in disease states (diabetic patients treated for osteomyelitis)
- Longer duration of treatment
- Inclusion of patients with stable renal function at baseline

Limitations
- Single centered, retrospective, small study
- Study failed to achieve power
- Heterogeneity between number of patients on VPT vs. VC

Authors

Conclusion
- Although no statistical difference was found in the rates AKI between groups and in the subgroup analysis, VPT-treated patients did develop AKI

Take Home Points
- Diabetic patients with higher risk of renal insufficiency at baseline
- Too many confounding variables to conclude confirmed AKI
Objective

- To evaluate the observed incidence of AKI in adult patients receiving either piperacillin-tazobactam and vancomycin (VPT) or cefepime-vancomycin (VC) for more than 48 hours, without preexisting renal insufficiency.

Design

- Single-center, retrospective matched cohort study (January 21, 2012 - October 15, 2012)

Population

Inclusion

- Men or women aged ≥ 18 years, who had a baseline Scr within 24 hours of admission
- Patients with at least one VM trough level, and had received treatment with VPT or VC for at least 48 hours during admission
- The combination of these agents was initiated no more than 48 hours apart

Exclusion

- Patients currently receiving dialysis, history of CKD (stage III or higher) or structural kidney disease (e.g., one kidney, kidney transplant, kidney tumor), or renal insufficiency (CrCl < 60 ml/min at admission)
- Current pregnancy, incarceration, treatment with investigational medications or ≥ one dose of intermittent (> 30 min) PT infusion
- Febrile neutropenia and meningitis infections

Outcomes

Primary endpoint

- Rates of AKI for patients treated between both arms according to the Acute Kidney Injury Network (AKIN) guidelines during therapy or within 72 hours after combination therapy was discontinued

Secondary endpoints

- Time to AKI from initiation of combination therapy and hospital length of stay (LOS)

Statistical Analysis

- Nonparametric Wilcoxon rank sum, Chi-square test or Fisher exact test for categorical data
- n= 112 patients per group was required to achieve a statistical power of 80% to detect a 15% difference between the VPT group (25%) and VC group (10%)
- Propensity score to control for potential bias and balance observed covariates among the two groups
- Greedy matching algorithm to match patients with comparable propensity scores

Results

Baseline Characteristics

- 643 records reviewed
- n=224; VPT=112, VC=112

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VPT (n=112)</th>
<th>VC (n=112)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>52.42± 13.91</td>
<td>50.37 ± 14.27</td>
<td>0.344</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.54± 26.33</td>
<td>83.15± 27.76</td>
<td>0.004</td>
</tr>
<tr>
<td>$S_c$ at start of antibiotics (mg/dl)</td>
<td>0.79± 0.24</td>
<td>0.74 ±0.22</td>
<td>0.413</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>39 (34.8)</td>
<td>60 (53.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Nephrotoxin (NSAIDs), n (%)</td>
<td>12 (10.7)</td>
<td>25 (22.3)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>VPT (n=39)</th>
<th>VC (n=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest VM trough prior to AKI (mcg/ml)</td>
<td>22.6</td>
<td>24.3</td>
<td>0.52</td>
</tr>
<tr>
<td>In ICU at AKI onset, n (%)</td>
<td>11 (28.2)</td>
<td>9 (64.3)</td>
<td>0.017</td>
</tr>
<tr>
<td>Days to AKI from Combination start, mean</td>
<td>4.97± 3.1</td>
<td>4.85± 2.9</td>
<td>0.975</td>
</tr>
<tr>
<td>Total days of AKI, mean outcome of AKI at discharge</td>
<td>7.6± 6.8</td>
<td>10± 14.8</td>
<td>0.0626</td>
</tr>
<tr>
<td>Resolved, n (%)</td>
<td>16 (41)</td>
<td>3 (21.4)</td>
<td>0.190</td>
</tr>
<tr>
<td>Insult still present, n (%)</td>
<td>23 (59)</td>
<td>11 (78.6)</td>
<td>0.190</td>
</tr>
</tbody>
</table>

- Unmatched data, the incidence of AKI was higher in the VPT (34.8%) versus VC (12.5%), (OR 3.74, 95% CI 1.89-7.39); p<0.0001
- Matched data:
  - n=110; VPT=55, VC=55
  - Propensity scores were estimated using age, weight, $S_c$, and estimated Clcr at baseline and antibiotics, admission unit and service, comorbidities, Charlson Comorbidity index, antibiotics allergies and indication
  - Incidence of AKI higher in the VPT (36.4%) versus VC (10.9%), (OR 5.67, 95% CI 1.66-19.33); p=0.003

Strengths

- Large study
IV. SUMMARY OF LITERATURE

A. Study limitations
   i. Retrospective, unblinded studies
   ii. Lack of randomization
   iii. Lack of power or inability to achieve power
   iv. Heterogeneity in patient groups

V. LITERATURE BASED CONCLUSION

A. AKI developed from the combination VPT therapy is reversible
B. While the data supporting the incidence of AKI with VPT therapy is limited, the risk of AKI may be higher in:
   a. Patient with higher acuity of illness
   b. Patients on combination VPT therapy for ≥ 4 days
C. Antibiotic de-escalation by day 3, is imperative to decrease the risk of AKI
D. Larger, randomized, multicenter trials are needed to provide further evidence of harm
REFERENCES

Appendix A:

Table 1: CHARLSON COMORBIDITY INDEX SCORING SYSTEM

<table>
<thead>
<tr>
<th>COMORBIDITY COMPONENT</th>
<th>Score</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Myocardical infarction (history, not ECG changes only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral vascular disease (includes aortic aneurysm ≥6cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cerebrovascular disease: CVA with mild or no residual or TIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic Pulmonary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild liver disease (without portal hypertension, includes chronic hepatitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes without end-organ damage (excludes diet-controlled alone)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hemiplegia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate or severe renal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes with end-organ damage (retinopathy, neuropathy, or brittle diabetes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor without metastases (exclude if &gt;5 years from diagnosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukemia (acute or chronic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Moderate or severe liver disease</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Metastatic solid tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIDS (not just HIV positive)</td>
</tr>
</tbody>
</table>

AGE

<table>
<thead>
<tr>
<th>Score</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;40</td>
</tr>
<tr>
<td>1</td>
<td>41-50</td>
</tr>
<tr>
<td>2</td>
<td>51-60</td>
</tr>
<tr>
<td>3</td>
<td>61-70</td>
</tr>
<tr>
<td>4</td>
<td>71-80</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.