Acute Kidney Injury with Antibiotic Combinations and Monotherapy

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Disclosures

• I have no financial disclosures to provide.

• I think the kidneys are exceptionally greedy and self-centered.
  – 20-25% blood flow
  – Mechanism for >50% of drugs cleared
  – One kidney can almost do the work of two if necessary (e.g., transplant, renal cell carcinoma)
Pharmacist Objectives

• Describe classification systems for acute kidney injury (AKI) and chronic kidney disease

• Examine potential patient and medication factors associated with AKI development

• Evaluate the potential impact of single and combination antibiotic therapy on AKI development
Technician Objectives

• Describe classification systems for AKI and chronic kidney disease

• Explain the importance of AKI on patient morbidity and mortality outcomes

• Discuss which medications are associated with AKI development
Agenda

AKI
- Definitions
- Epidemiology

Vancomycin
- Risk factors
- Management

Piperacillin-tazobactam
- Mechanism
- Non-critically ill
- Critically ill

Polymyxins
- Mechanisms
- Dosing strategies
Estimating Kidney Function

• What do we want to know?
  – How much volume is moving through the glomerulus over a specific time (e.g., minute)

• How do we measure this?
  – In the lab → inulin
    • Freely filtered
    • No tubular secretion or reabsorption
    • No non-renal clearance
  – In the real world → serum creatinine (SCr)
Serum Creatinine

• “Because it’s the hero patients deserve, but not the one they need.” – Lt. James Gordon (adapted to the renal world)

• Muscle production + renal excretion
• Filtered + secreted into renal tubules
• Unpredictable steady-state
  – Changes in above + volume of distribution and elimination rate
Modification of Diet in Renal Disease

• Validated in African American and Caucasian 18-70 year olds with stable CKD

• When GFR > 60 mL/min/1.73 m², MDRD underestimates true GFR

• Avoid if unstable SCr, high/low muscle mass

• $GFR = 186 \times SCr^{-1.154} \times age^{-0.203} \times 1.212 \ (if \ AA) \times 0.742 \ (if \ female)$

Cockcroft-Gault

- Validated in Caucasians 18-92 years old with varying renal functions
- May overestimate GFR by 5-20% (more so when decreased GFR)
- Use IBW unless (morbidly) obese, then AdjBW
- Avoid if unstable SCR, high/low muscle mass
- CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * SCR)

Types of AKI

- Prerenal AKI
- Postrenal AKI

Intrinsic AKI
- Glomerular Injury
- Tubulointerstitial
- Tubular obstruction

Diagram showing the renal system with labels for Renal Artery, Renal Pelvis, Ureter, Bladder, Urethra, and a breakdown of renal structures.
AKI Complicates Matters

- Difficult to achieve steady-state for SCr
- Increase in secretion of creatinine in early AKI
- Treatment (e.g., IV fluids, renal replacement therapy) affects volume of distribution

- How is the extent of AKI determined?
## Criteria for AKI

### RIFLE Class

<table>
<thead>
<tr>
<th>RIFLE Class</th>
<th>SCr/GFR Criteria</th>
<th>UOP Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>↑ SCr 1.5-fold or &gt;25% ↓ GFR</td>
<td>&lt;0.5 mL/kg/hr x6 hr</td>
</tr>
<tr>
<td>Injury</td>
<td>↑ SCr 2-fold or &gt;50% ↓ GFR</td>
<td>&lt;0.5 mL/kg/hr x12 hr</td>
</tr>
<tr>
<td>Failure</td>
<td>↑ SCr 3-fold, SCr ≥4 mg/dL, or &gt;75% ↓ GFR</td>
<td>&lt;0.3 mL/kg/hr x24 hr or anuria x12 hr</td>
</tr>
<tr>
<td>Loss</td>
<td>Complete loss &gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>Complete loss &gt;3 months</td>
<td></td>
</tr>
</tbody>
</table>

### AKIN Stage

<table>
<thead>
<tr>
<th>AKIN Stage</th>
<th>SCr Criteria</th>
<th>UOP Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>↑ SCr 1.5- to 2-fold above baseline or 0.3 mg/dL</td>
<td>&lt;0.5 mL/kg/hr x6 hr</td>
</tr>
<tr>
<td>Injury</td>
<td>↑ SCr 2- to 3-fold above baseline</td>
<td>&lt;0.5 mL/kg/hr x12 hr</td>
</tr>
<tr>
<td>Failure</td>
<td>↑ SCr &gt;3-fold above baseline or SCr ≥4 mg/dL with acute ↑ ≥0.5 mg/dL</td>
<td>&lt;0.3 mL/kg/hr x24 hr or anuria x12 hr</td>
</tr>
</tbody>
</table>

AKI Epidemiology

- Community AKI
  - 1% to 2%

- Hospital (non-ICU) AKI
  - 2% to 20%

- Critically ill (ICU) AKI
  - 20% to 60%

Antimicrobials Associated with AKI

- Vancomycin (ATN...probably)
- Aminoglycosides (ATN)
- Polymyxins (ATN)
- Penicillins (AIN)
- Sulfamethoxazole/trimethoprim (crystalline obstruction)
- Acyclovir (crystalline obstruction)
- Amphotericin B (ATN)

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- Dosing strategies
Vancomycin Mechanism of Nephrotoxicity

Renal tubular ischemia following oxidative effects on proximal renal tubule cells

- May depend on energy-dependent transport process from blood to tubular cells across basolateral membrane
- Changes the energy-dependent renal absorption function
- Alters mitochondrial function

Patient Case

- 24 y/o WM presents from home with redness, indurated skin and pus surrounding a PICC
- Patient left AMA from ED 5 days prior (acute intoxication, eager medical intern inserted line)
- MRSA nasal swab previously taken in ED was +, so attending wants to begin vancomycin 1.5 g IV Q8H
- ABW 112 kg, BMI 41, SCr 0.6 mg/dL, Tmax 39.2 C
Patient Case

Assuming no other nephrotoxic medications are prescribed and the physician wants to target a trough concentration 15-20 mg/L and treat for 14+ days, which are risk factors for vancomycin-associated nephrotoxicity?

A. ABW > 101.4 kg
B. Daily dose >4 g
C. Serum trough ≥15 mg/L
D. Duration >7 days
Vancomycin Orders per Institution

At my hospital, pharmacists are involved in dosing vancomycin by means of...

A. Pharmacokinetic consult ordered by providers
B. Recommendations provided on rounds
C. Recommendations provided at time of order verification
D. Recommendations provided <25% of orders
My Hospital Doses Vancomycin...

A. Nomogram (based on weight and renal function)
B. Pharmacokinetics calculator (e.g., MedCalc, GlobalRPH, in-house build)
C. Manual calculations
D. 15-20 mg/kg/dose + renal function-dependent frequency
E. Predominately provider-dependent ordering
Vancomycin-Associated Nephrotoxicity

• “Mississippi mud” in clinical use since 1958

Vancomycin-Associated Nephrotoxicity

- FDA-approved regimen; VAN <3%
  - 1 g IV Q12H
  - Targeted serum trough 5-10 mg/L

- Otherwise, VAN incidence 5-43%
  - Presence of risk factors
  - Predominately reversible

Vancomycin Doses ≥4 g/day

- Single-center, retrospective cohort study
- Vancomycin <4 g/day → 200 patients
- Vancomycin ≥4 g/day → 26 patients
- Linezolid → 45 patients
- Adults who received ≥48 hours of vancomycin throughout the hospital

Vancomycin Doses ≥4 g/day

- Vancomycin <4 g/day → 10.9%
- Vancomycin ≥4 g/day → 34.6%
- Linezolid → 6.7%

Final Logistic Regression Model for Occurrence of Nephrotoxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose ≥4 g/day</td>
<td>4.4</td>
<td>1.7 – 11.8</td>
<td>0.003</td>
</tr>
<tr>
<td>ABW ≥101.4 kg</td>
<td>3.4</td>
<td>1.5 – 7.9</td>
<td>0.004</td>
</tr>
<tr>
<td>CrCl ≤86.6 mL/min</td>
<td>3.7</td>
<td>1.2 – 11.5</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU residence</td>
<td>2.2</td>
<td>1.4 – 4.6</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Vancomycin Doses $\geq 4$ g/day

Vancomycin Doses $\geq 4$ g/day

Summary

- Weak strength-of-evidence
- Recent trials have minimal patients $\geq 4$ g/day
  - Inhibits ability to reassess this risk factor

More evidence for effects of vancomycin dosing on serum concentrations...
Vancomycin Trough $\geq 15$ mg/L

- Increased presence of vancomycin may increase extent of acute tubular necrosis
- Initial trough and at-anytime trough values have been investigated
- Most patients in studies evaluating the impact of troughs have multiple risk factors for VAN

Vancomycin Trough $\geq 15$ mg/L

### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High troughs $\geq 15$mg/L</th>
<th>Low trough &lt;15mg/L</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso et al. (21)</td>
<td>42</td>
<td>142</td>
<td>4.30 [2.19, 8.43]</td>
</tr>
<tr>
<td>Cano et al. (22)</td>
<td>22</td>
<td>89</td>
<td>4.32 [1.74, 10.69]</td>
</tr>
<tr>
<td>Chung et al. (23)</td>
<td>12</td>
<td>25</td>
<td>1.85 [0.69, 4.96]</td>
</tr>
<tr>
<td>Hermse et al. (30)</td>
<td>5</td>
<td>16</td>
<td>3.98 [0.91, 17.46]</td>
</tr>
<tr>
<td>Hidayat et al. (13)</td>
<td>11</td>
<td>63</td>
<td>14.24 [0.81, 249.87]</td>
</tr>
<tr>
<td>Jeffres et al. (15)</td>
<td>27</td>
<td>49</td>
<td>3.02 [1.28, 7.11]</td>
</tr>
<tr>
<td>Kralovska et al. (31)</td>
<td>21</td>
<td>60</td>
<td>2.02 [1.04, 3.96]</td>
</tr>
<tr>
<td>Kullar et al. (32)</td>
<td>8</td>
<td>116</td>
<td>6.15 [0.75, 50.13]</td>
</tr>
<tr>
<td>Kullar et al. (8)</td>
<td>27</td>
<td>139</td>
<td>1.24 [0.67, 2.28]</td>
</tr>
<tr>
<td>Lodise et al. (36)</td>
<td>7</td>
<td>27</td>
<td>3.13 [1.12, 8.69]</td>
</tr>
<tr>
<td>McKenny et al. (38)</td>
<td>16</td>
<td>57</td>
<td>4.98 [1.98, 12.52]</td>
</tr>
<tr>
<td>Minejima et al. (39)</td>
<td>17</td>
<td>72</td>
<td>1.61 [0.80, 3.21]</td>
</tr>
<tr>
<td>Prabaker et al. (43)</td>
<td>7</td>
<td>54</td>
<td>1.68 [0.68, 4.11]</td>
</tr>
<tr>
<td>Wunderink et al. (50)</td>
<td>26</td>
<td>118</td>
<td>2.25 [1.22, 4.13]</td>
</tr>
<tr>
<td>Zimmermann et al. (51)</td>
<td>8</td>
<td>12</td>
<td>1.00 [0.19, 5.19]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|            | 1039                        | 1718               | 2.67 [1.95, 3.65]              |

Total events 256, 201

Heterogeneity: Tau² = 0.14; Chi² = 23.89, df = 14 (P = 0.05); I² = 41%

Test for overall effect: Z = 6.13 (P < 0.00001)

Initial Vancomycin Trough ≥15 mg/L

### Vancomycin Trough & Hospital Location

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ICU residence</th>
<th>Ward patients</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso et al. (21)</td>
<td>23/55</td>
<td>73/233</td>
<td>1.58 [0.86, 2.88]</td>
</tr>
<tr>
<td>Lodise et al. (36)</td>
<td>14/21</td>
<td>56/145</td>
<td>3.18 [1.21, 8.36]</td>
</tr>
<tr>
<td>McKamy et al. (38)</td>
<td>22/24</td>
<td>77/143</td>
<td>9.43 [2.14, 41.60]</td>
</tr>
<tr>
<td>Minejima et al. (39)</td>
<td>20/70</td>
<td>23/157</td>
<td>2.33 [1.18, 4.61]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>170/229</strong></td>
<td><strong>678/100.0%</strong></td>
<td><strong>2.57 [1.44, 4.58]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.15; Chi² = 5.57, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 3.20 (P = 0.001)

Vancomycin Trough $\geq 15$ & $\geq 20$ mg/L

Patient Case

Assuming no other nephrotoxic medications are prescribed and the physician wants to target a trough concentration 15-20 mg/L and treat for 14+ days, which are risk factors for vancomycin-associated nephrotoxicity?

A. ABW > 101.4 kg
B. Daily dose > 4 g
C. Serum trough ≥ 15 mg/L
D. Duration > 7 days
Vancomycin Trough $\geq 15$ mg/L

Summary

- Most episodes occurred after 7 days of therapy
- Increased incidence in critically ill
- Any trough $\geq 15$ mg/L may increase risk of VAN
  - Seen after multivariate analyses
  - More pronounced when trough $\geq 20$ mg/L

Do other nephrotoxic medications impact AKI?
Agenda

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- Mechanisms
- Dosing strategies
Patient Case

- Blood cultures resulted MRSA
- Vancomycin 1.5 g IV Q8H → Trough 15.2 mg/L
- RN found patient with respiratory compromise and fever (38.9 C) at 0500
  - Significant other snuck alcohol from home to patient
- CXR with bilateral infiltrates in both lungs
  - Suspected aspiration overnight
- Physician would like to intubate, begin piperacillin/tazobactam (PTZ), and admit to ICU
Patient Case

Assuming the patient will continue to receive vancomycin in addition to PTZ, which are risk factors for nephrotoxicity with the combination?

A. Concomitant use of vancomycin & PTZ
B. Daily dose of PTZ
C. Length of infusion (intermittent vs. extended)
D. Critical illness
My Hospital Doses PTZ...

A. Intermittent infusion (30 minutes) in all settings
B. Extended infusion (4 hours) in all settings
C. Extended infusion (4 hours) in ICU settings
D. Continuous infusion in some settings
Concomitant Nephrotoxic Medications

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Receipt of NTs</th>
<th>no NTs</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bosso et al. (21)</td>
<td>26</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>Cano et al. (22)</td>
<td>16</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Hidayat et al. (13)</td>
<td>10</td>
<td>11</td>
<td>17</td>
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<td>Kralovicova et al. (31)</td>
<td>31</td>
<td>134</td>
<td>19</td>
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<tr>
<td>Lodise et al. (36)</td>
<td>6</td>
<td>21</td>
<td>55</td>
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<td>18</td>
<td>24</td>
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</tr>
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<td>Minejima et al. (39)</td>
<td>37</td>
<td>169</td>
<td>6</td>
</tr>
<tr>
<td>Prabaker et al. (43)</td>
<td>21</td>
<td>31</td>
<td>174</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>474</td>
<td>1203</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>165</td>
<td>392</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.54; Chi² = 60.99, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.50 (P = 0.01)

Acute Interstitial Nephritis

- Characterized by inflammatory infiltrate localizing in renal interstitium
- Most common cause is exposure to beta-lactam antibiotics
  - Antistaphylococcal penicillins (large case series)
  - Antipseudomonal beta-lactams (case reports)
- Definitive diagnosis from kidney biopsy

Vancomycin + PTZ

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Patients</th>
<th>Dosing</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meaney (2014)</td>
<td>125 non-ICU</td>
<td>No info</td>
<td>22.4% AKI, OR 5.36, p&lt;0.05</td>
</tr>
<tr>
<td>Moenster (2014)</td>
<td>129 non-ICU</td>
<td>22% on 18 g/day; 78% &lt;18 g/day</td>
<td>18 g: 29.3% vs. 13.3%, p=0.09 &lt;18 g: 37.5% vs. 17.6%, p=0.29 OR 3.45, 95% CI 0.96-12.4, p=0.057</td>
</tr>
<tr>
<td>Burgess (2014)</td>
<td>191 (&lt;20% ICU)</td>
<td>No info</td>
<td>16.3% vs. 8.1%, p=0.041</td>
</tr>
<tr>
<td>Sutton (2015)</td>
<td>108 (&lt;20% ICU)</td>
<td>No info</td>
<td>21.3% vs. 4.5%, OR 3.97, p=0.002</td>
</tr>
<tr>
<td>Gomes (2014)</td>
<td>224 (50% ICU)</td>
<td>13.5 g/day*</td>
<td>36.4% vs. 10.9%, p=0.003</td>
</tr>
<tr>
<td>Hammond (2015)</td>
<td>122 ICU</td>
<td>13.5-18 g/day**</td>
<td>32.5% vs. 41.8%, p=0.078</td>
</tr>
</tbody>
</table>

*Extended infusion
**Intermittent infusion

• 139 diabetic patients with osteomyelitis
  – 109 vancomycin + PTZ
    • 32 high-dose (PTZ ≥18 g/day)
  – 30 vancomycin + cefepime
    • 17 high-dose (cefepime ≥3 g/day)

• High-dose therapy OR 1.45 (p=0.45)

• Underpowered to assess AKI

P=0.06 for PTZ vs. cefepime for AKI

PTZ Length of Infusion

- 200 patients received PTZ
  - 100 intermittent infusion (over 30 minutes)
    - 35% concomitant vancomycin
    - 11% AKI
  - 100 extended infusion (over 4 hours)
    - 27% concomitant vancomycin
    - 9% AKI

- Resident project (2012); significant data points missing

- No difference in rate of AKI (p=0.637)

PTZ in Critical Illness

• 50% of 224 patients received care in ICU
  – PTZ (extended infusion) vs. cefepime – high-dose
  – No subgroup analysis of ICU patients

• Propensity score matching yielded 55 pairs
  – Analysis of these pairs

• Increased AKI with vancomycin + PTZ
  – (36.4% vs. 10.9%, p=0.003)

PTZ in Critical Illness

• 122 patients received vancomycin and beta-lactam
  – 49 PTZ and 73 cefepime
  – Similar vancomycin trough (17.9 vs. 15.1 mg/L, p=0.11) and concurrent nephrotoxins (1.08 vs. 1.01, p=0.56)

• Propensity score matching yielded 43 pairs (71%)

• No difference in AKI (32.5% vs. 41.8%, p=0.078)
Patient Case

Assuming the patient will continue to receive vancomycin in addition to PTZ, which are risk factors for nephrotoxicity with the combination?

A. Concomitant use of vancomycin & PTZ
B. Daily dose of PTZ
C. Length of infusion (intermittent vs. extended)
D. Critical illness
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Patient Case

- Patient has remained febrile x3 days with worsening oxygenation

- Bronchoalveolar lavage culture grows extended-drug resistant *Acinetobacter baumannii*
  - Ampicillin/sulbactam (R), meropenem (I), polymyxin (S)

- Physician would like to begin meropenem IV and an inhaled and IV polymyxin product
  - Polymyxin product/dosing per pharmacy
My Hospital Uses...

A. Polymyxin E (Colistimethate) for IV use
B. Polymyxin B for IV use
C. Polymyxin E (Colistimethate) for inhaled use
D. Polymyxin B for inhaled use
E. No inhaled polymyxin products
Polymyxins Basics

• Cyclic decapeptides linked to a fatty acid chain
  – Polymyxin E: D-leucine, L-threonine and L-αγ-diaminobutyric acid
  – Polymyxin B contains D-phenylalanine instead of D-leucine

• Compete and displace Ca$^{2+}$ and Mg$^{2+}$ ions
  – Local disturbance of the cell membrane
  – Increased cell permeability
  – Leakage of the cell content, cell lysis and death

• Neutralize lipopolysaccharide molecules of Gram-negative bacteria cell membranes, providing anti-endotoxin activities
Polymyxins Basics

• Considerable distribution into tissues

• Polymyxin B
  – Highly protein bound in critically ill (79-92%)
  – Metabolism by unknown methods
  – Non-renal clearance; increased reabsorption with higher CrCl rates

• Polymyxin E
  – Inactive drug (colistimethate sodium) hydrolyzed to active drug (colistin)
  – Colistimethate excreted unchanged (60%)
  – Colistin with extensive reabsorption and non-renal clearance

Polymyxins Nephrotoxicity

- Colistimethate sodium (5 mg/kg/day or 150 mg every 12 hours) and polymyxin B (1.5–2.5 mg/kg/day as a continuous infusion) in 173 critically ill patients
- Less AKI with polymyxin B (41.8% vs. 60.4%, p=0.02)
  - 7 colistimethate sodium patients with loss of renal function

Polymyxin B Nephrotoxicity

- In a study of 276 critically ill patients, ≥ 200 mg polymyxin B independently associated with...

- Protection from in-hospital mortality
  - OR 0.43, 95% CI 0.23-0.79, p=0.007

- Severe renal impairment (reversible)
  - OR 4.51; 95% CI 1.58–12.9; p = 0.005

Polymyxin B (IV)
- Loading dose: 2.5 mg/kg IV (TBW) – 280 mg x1
- Maintenance dose: 1.5 mg/kg IV (TBW) Q12H – 160 mg Q12H

Colistimethate sodium (inhaled)
- 2.5 mg/kg/day divided Q6-8H – 70 mg inhaled Q6H

Summary

• Risk factors exists for VAN
  – Target trough 15-20 mg/L
  – Duration ≥7 days
  – Concomitant nephrotoxic medications

• Piperacillin/tazobactam may increase AKI
  – Likely AIN mechanism
  – Uncertain on dose or infusion type as factors

• Polymyxin B is less nephrotoxic than Colistin
Acute Kidney Injury with Antibiotic Combinations and Monotherapy

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University of Arkansas for Medical Sciences
References


References

References

### TABLE 3 Primary and secondary outcomes of patients receiving vancomycin product

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pfizer drug recipients (n = 146)</th>
<th>Hospira drug recipients (n = 146)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary, by definition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consensus vancomycin guideline</td>
<td>13 (8.9)</td>
<td>16 (11)</td>
<td>0.56</td>
</tr>
<tr>
<td>AKIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stages</td>
<td>25 (17.1)</td>
<td>19 (13)</td>
<td>0.33</td>
</tr>
<tr>
<td>Stage 1</td>
<td>12 (8.2)</td>
<td>3 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>12 (8.2)</td>
<td>12 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>1 (0.7)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td>RIFLE</td>
<td></td>
<td></td>
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<tr>
<td>All stages</td>
<td>15 (10.3)</td>
<td>17 (11.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Risk</td>
<td>6 (4.1)</td>
<td>8 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>8 (5.5)</td>
<td>5 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>1 (0.7)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy required</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>5 (3.4)</td>
<td>9 (6.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Length of stay (mean days [range])</td>
<td>10 (6–18)</td>
<td>11 (7–17)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

### TABLE 4 Predictors of nephrotoxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bivariate analysis(^a)</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Receipt of Hospira vancomycin</td>
<td>1.15</td>
<td>0.55–2.40</td>
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<tr>
<td>Concomitant piperacillin-tazobactam</td>
<td>5.17</td>
<td>2.29–11.66</td>
</tr>
<tr>
<td>Vancomycin trough of &gt;20 mg/liter</td>
<td>4.54</td>
<td>2.09–9.90</td>
</tr>
<tr>
<td>Severe sepsis/septic shock</td>
<td>4.51</td>
<td>1.54–13.26</td>
</tr>
<tr>
<td>Receipt of ≥2 concomitant nephrotoxins</td>
<td>4.22</td>
<td>1.96–9.06</td>
</tr>
<tr>
<td>Vancomycin loading dose of ≥20 mg/kg</td>
<td>0.52</td>
<td>0.25–1.10</td>
</tr>
</tbody>
</table>

\(^a\) OR, odds ratio; CI, confidence interval.