(292-L01) Contemporary Considerations: Cutting-Edge Advances in Vancomycin Therapy

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Thomas Lodise, PharmD, PhD
Michael J. Rybak, Pharm.D., MPH, FCCP
Manjunath (Amit) Pai, PharmD
Disclosure

The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

- **Manjunath (Amit) Pai** - Astellas Pharma, Inc.: Consultant; Melinta Therapeutics: Consultant; Theravance Biopharma: Board Member/Advisory Panel

- **Marc Scheetz** - Merck: Grant/Research Support; Premier; Speaker's Bureau
<table>
<thead>
<tr>
<th>Start Time</th>
<th>End Time</th>
<th>Presentation</th>
<th>Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>8:25 AM</td>
<td>Updates to literature and research surrounding</td>
<td>Marc H. Scheetz, Pharm.D., M.Sc., BCPS-AQ ID</td>
</tr>
<tr>
<td>8:25 AM</td>
<td>8:50 AM</td>
<td>Understand the updates to Vancomycin Ph...</td>
<td>Thomas Lodise, PharmD, PhD</td>
</tr>
<tr>
<td>8:50 AM</td>
<td>9:15 AM</td>
<td>Interactive Debate: Vancomycin is Clinically...</td>
<td>Michael J. Rybak, Pharm.D., MPH, FCCP</td>
</tr>
<tr>
<td>9:15 AM</td>
<td>9:40 AM</td>
<td>Interactive debate. Vancomycin is clinically...</td>
<td>Manjunath (Amit) Pai, PharmD</td>
</tr>
<tr>
<td>9:40 AM</td>
<td>9:45 AM</td>
<td>QA</td>
<td>Marc H. Scheetz, Pharm.D., M.Sc., BCPS-AQ ID; T...</td>
</tr>
</tbody>
</table>
Vancomycin: PK/PD Toxicity. A Focus on Nephrotoxicity.

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Northwestern Medicine
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Disclosure

• I submit the following disclosures:

  • I have received honoraria for speaking by Premier, Inc.

  • I am a currently a funded study investigator for the NIH (multiple studies) and the CARE Foundation.

  • I have previously received salary support from Merck/Cubist (2015) for an antimicrobial stewardship study and the State of Illinois for an organism virulence study (2016).

  • I have solicited an educational grant from Allergan (2016, no personal remuneration).

• The views offered in the presentation are not necessarily the views of Midwestern University, Northwestern Memorial Hospital, or any other affiliated organizations.
Overview

- Historical Review
  - Clinical and Laboratory Data
- Returning to ‘Pre’- Clinical Data
- Minimization of Toxicity, Dosing Strategies?
Does vancomycin cause nephrotoxicity?

A. Yes, it causes kidney damage.
B. No, it is correlated with damage, but those studies are flawed.
C. No, I have given this drug thousands of times and have never seen nephrotoxicity.
Historical Review
Vancomycin and Toxicities

- Ototoxicity
- Neurotoxicity
- Nephrotoxicity... where we will spend our time.
  - Acute kidney injury (AKI) is a significant and preventable cause of excess morbidity.
  - AKI prevalent among critically ill, hospitalized patients
  - Of approximately 1.8 million persons affected annually, ~20% AKI cases are thought to be drug-related.
  - AKI associated with increased mortality, greater LOS

Vancomycin and Kidney Injury... 1950’s to current.

Vancomycin Nephrotoxicity Manuscripts

Scheetz MH. Pubmed Search 071715. Keywords "Vancomycin" and "Nephrotoxicity"
Circa 1950s

- MRSA non-existent
  - Quickly shelved.... Semi-synthetic penicillins treat PCN-resistant *S.aureus*
- New drug. Impure
  - “A *pyrogen reaction* with chills and high fever occurred not infrequently with the early batches of vancomycin, and often this reaction appeared just 1 hour after the injection. This type of reaction was relatively infrequent with later batches of vancomycin.”
- Early realizations. Partially correct.
  - “In patients with azotemia or renal insufficiency vancomycin should be used with caution and in smaller doses, and *therapy should be guided by repeated serum assays*.... This is to insure that high serum levels of vancomycin do not develop in these patients.... *Assays need NOT be done in young patients with normal renal function*....We think the level should be kept below 30 to 40mcg/mL except in unusual circumstances.”
  - Concern for cochleotoxicity and vestibulotoxicity
  - Out of 85 patients, all suffered some phlebitis.


- Vancomycin is now crystalline and pyrogen-free
- Nephrotoxicity is infrequent (~5%); concomitant nephrotoxins (e.g. aminoglycosides potentiate ~35% ¹)
- Rat study: up to 400 mg/kg SQ over 28 days without kidney damage, however, histological changes are seen in dose dependent fashion. ²
  - Serum concentrations were not obtained
- Second study corroborates SQ rat data and low kidney injury, but....³
  - Dogs: LD₅₀ is 292 mg/kg IV, secondary to renal failure (allometry equivalent: 162 mg/kg).
  - Dogs: Long term studies show slight renal damage in 4/22 dogs receiving 50 mg/kg IV (allometry equivalent: 28 mg/kg)

**The Original “Eli Lilly” Data: Intra-Peritoneal**

Evaluation of renal function in rats given combinations of vancomycin and tobramycin.

<table>
<thead>
<tr>
<th>Vancomycin (mg/kg)</th>
<th>Tobramycin (mg/kg)</th>
<th>BUN (mg/dl)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Gluconeogenesis (µg/g per hr)</th>
<th>NAG (µmoles substrate/min)</th>
<th>Relative kidney weight (g/100g of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>21 ± 1</td>
<td>0.5 ± 0.1</td>
<td>18 ± 2</td>
<td>2.3 ± 1.2</td>
<td>0.90 ± 0.02</td>
</tr>
<tr>
<td>75</td>
<td>0</td>
<td>19 ± 1</td>
<td>0.6 ± 0.0</td>
<td>23 ± 3</td>
<td>8.9 ± 2.5</td>
<td>0.97 ± 0.04</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
<td>26 ± 3</td>
<td>0.7 ± 0.1</td>
<td>18 ± 2</td>
<td>14.4 ± 4.7</td>
<td>1.20 ± 0.09</td>
</tr>
<tr>
<td>0</td>
<td>60</td>
<td>25 ± 1</td>
<td>0.4 ± 0.0</td>
<td>22 ± 5</td>
<td>24.6 ± 3.7</td>
<td>0.98 ± 0.02</td>
</tr>
<tr>
<td>75</td>
<td>60</td>
<td>32 ± 3</td>
<td>0.6 ± 0.3</td>
<td>17 ± 2</td>
<td>45.2 ± 5.5</td>
<td>1.15 ± 0.04</td>
</tr>
<tr>
<td>150</td>
<td>60</td>
<td>31*</td>
<td>4.0 ± 1.0*</td>
<td>7 ± 4*</td>
<td>123 ± 43*</td>
<td>1.31 ± 0.04*</td>
</tr>
</tbody>
</table>

NOTE: Vancomycin doses were administered IP BID x 4D; tobramycin was given SC BID x 4 days.

BUN = blood urea nitrogen; NAG = N-acetyl-ß-glycosaminidase.

150/6.2 = 24.2 mg/kg

Significant (i.e. p<0.05)
The Doubt?

• Vancomycin causes very little nephrotoxicity?
  o Cantu et al.\textsuperscript{1} Summarizes 82 cases in the literature.
    ➢ 41 receiving concomitant aminoglycosides
    ➢ 20 had other explanatory reasons for injury
    ➢ 18 did not sufficiently detail if other potential causes were present
    ➢ Only 3 patients received vancomycin monotherapy.\textsuperscript{1}

• Chicken or the Egg? Which came first, nephrotoxicity or high troughs?

• It is realized that prospective studies are needed.

Defining Nephrotoxicity

**RIFLE**

- **Risk**
  - Increased Cr x 1.5 or GFR decreases >25%

- **Injury**
  - Increased Cr x 2 or GFR decreases >50%

- **Failure**
  - Increased Cr x 3 or GFR decreases >75% or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)

- **Loss**
  - Persistent ARF = complete loss of renal function for > 4 weeks

- **ESRD**
  - End Stage Renal Disease

- **Urine Output (UO) Criteria**
  - UO < 0.5 ml/kg/hr x 6 hr
  - UO < 0.3 ml/kg/hr x 24 hr or anuria x 12 hr

**AKIN**

- **Stage 1**
  - Increased Cr x 1.5 or ≥ 0.3 mg/dl
  - UO < 0.5 ml/kg/hr x 6 hr

- **Stage 2**
  - Increased Cr x 2
  - UO < 0.5 ml/kg/hr x 12 hr

- **Stage 3**
  - Increased Cr x 3 or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)
  - UO < 0.3 ml/kg/hr x 24 hr or anuria x 12 hr

Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

Cruz et al. Critical Care 2009
## Vanco Circa 2009: Time for a Change

Paraphrasing the “Expert Panel Recommendations for Vancomycin Therapeutic Drug Monitoring (TDM)”

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommendations</th>
<th>Level of Evidence and Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDM for Vancomycin-Induced Nephrotoxicity</strong></td>
<td>&gt;2 consecutive increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline) after several days of vancomycin therapy.</td>
<td>IIB</td>
</tr>
<tr>
<td>Definition</td>
<td>Data do not support using peak serum vancomycin concentrations to monitor for nephrotoxicity.</td>
<td>IIB</td>
</tr>
<tr>
<td>Criteria for monitoring</td>
<td>Trough monitoring is recommended</td>
<td>IIIB</td>
</tr>
<tr>
<td>Frequency of monitoring</td>
<td>Frequent monitoring is not recommended.</td>
<td>IIB</td>
</tr>
<tr>
<td>All patients receiving &gt;3 days should have at least one steady-state trough concentration obtained.</td>
<td>IIB</td>
<td></td>
</tr>
<tr>
<td>There are limited data supporting the safety of sustained trough concentrations of 15-20 mg/L. Once-weekly monitoring is recommended of hemodynamically stable patients. More frequent or daily trough monitoring is advisable in patients who are hemodynamically unstable.</td>
<td>IIIB</td>
<td></td>
</tr>
</tbody>
</table>
Modifiers of Vancomycin Kidney Injury... many papers, similar answers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>aOR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin ≥4 g/day</td>
<td>4.4</td>
<td>1.7-11.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Wt of ≤101.4 kg</td>
<td>3.4</td>
<td>1.5-7.9</td>
<td>0.004</td>
</tr>
<tr>
<td>CrCl level of ≤86.6 ml/min</td>
<td>3.7</td>
<td>1.2-11.5</td>
<td>0.020</td>
</tr>
<tr>
<td>ICU residence</td>
<td>2.2</td>
<td>1.1-4.6</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*Controlled for sex and contrast use*

Probability of serum creatinine (SCr) increase of 0.5 mg/dL

# Initial Clinical PK / Ptoxicity Evaluations

## Bivariate Analysis: Vancomycin and Nephrotoxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nephrotoxicity (n = 21)</th>
<th>No Nephrotoxicity (n = 145)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial mean vancomycin trough (mg/L) ± SD</td>
<td>14.6 ± 8.3</td>
<td>9.6 ± 5.1</td>
<td>0.014</td>
</tr>
<tr>
<td>Initial vancomycin trough value, ≥9.9 mg/L</td>
<td>16 (76.2)</td>
<td>56 (38.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24\text{ss}}$ value, mean mg x h/L ± SD</td>
<td>1318.4 ± 1147.2</td>
<td>898.5 ± 475.9</td>
<td>0.11</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24\text{ss}}$ value &gt;1300 mg x h/L</td>
<td>7 (33.3)</td>
<td>20 (13.8)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**NOTE:** $\text{AUC}_{0-24\text{ss}},$ vancomycin area under the curve from 0-24 h at steady state

## Logistic Regression, Nephrotoxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>aOR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial trough value</td>
<td>1.13 (1.05-1.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU</td>
<td>3.25 (1.18-8.97)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Lodise et al. Clinical Infectious Diseases 2009
Change Realized. Dose:Response

META-ANALYSIS: Nephrotoxicity rate is between 5 and 43%

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High troughs ≥15mg/L Events</th>
<th>Total</th>
<th>Low trough &lt;15mg/L Events</th>
<th>Total</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso et al. (21)</td>
<td>42</td>
<td>142</td>
<td>13</td>
<td>146</td>
<td>4.30</td>
<td>[2.19, 8.46]</td>
</tr>
<tr>
<td>Cano et al. (22)</td>
<td>22</td>
<td>89</td>
<td>7</td>
<td>99</td>
<td>4.32</td>
<td>[1.74, 10.69]</td>
</tr>
<tr>
<td>Chung et al. (23)</td>
<td>12</td>
<td>25</td>
<td>16</td>
<td>48</td>
<td>1.85</td>
<td>[0.69, 4.96]</td>
</tr>
<tr>
<td>Jeffres et al. (15)</td>
<td>27</td>
<td>49</td>
<td>13</td>
<td>45</td>
<td>3.02</td>
<td>[1.28, 7.11]</td>
</tr>
<tr>
<td>Kullar et al. (32)</td>
<td>8</td>
<td>116</td>
<td>1</td>
<td>84</td>
<td>6.15</td>
<td>[0.75, 50.13]</td>
</tr>
<tr>
<td>Kullar et al. (8)</td>
<td>27</td>
<td>139</td>
<td>23</td>
<td>141</td>
<td>1.24</td>
<td>[0.67, 2.28]</td>
</tr>
<tr>
<td>Lodise et al. (36)</td>
<td>7</td>
<td>27</td>
<td>14</td>
<td>139</td>
<td>3.13</td>
<td>[1.12, 8.69]</td>
</tr>
<tr>
<td>Zimmermann et al. (51)</td>
<td>8</td>
<td>12</td>
<td>0</td>
<td>33</td>
<td>126.56</td>
<td>[6.19, 2585.90]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>599</td>
<td></td>
<td>735</td>
<td></td>
<td>3.12</td>
<td>[1.81, 5.37]</td>
</tr>
<tr>
<td>Total Events</td>
<td>153</td>
<td></td>
<td>87</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A Prospective Look

- Study **took 5.5 yr**; 1,255 patients randomized to get to: **172 linezolid and 176 vancomycin patients** (Per Protocol analysis)

- Arguments about the baseline differences between the groups will be endless... but they were reasonably well matched.

- Vancomycin troughs at day 3 and pharmacists prospectively dosed and adjusted doses for patients based on renal function.

- Nephrotoxicity: 8.4% of Linezolid patients and 18.2% of vancomycin patients.

- Attributable vancomycin nephrotoxicity: ~10%
  - This assumes that we follow Historical Dosing Methods!

### Baseline Demographics and Clinical Characteristics of the Per-Protocol Population

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>LINEZOLID (n = 172)</th>
<th>VANCOMYCIN (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting condition, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (36.1)</td>
<td>74 (42.5)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>117 (68.0)</td>
<td>118 (67.1)</td>
</tr>
<tr>
<td>Kidney</td>
<td>48 (27.9)</td>
<td>65 (36.9)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>97 (56.4)</td>
<td>106 (60.2)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>60.7 (18.0)</td>
<td>61.6 (17.7)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>78.1 (23.3)</td>
<td>76.5 (21.8)</td>
</tr>
<tr>
<td>Mechanical ventilation, No. (%)</td>
<td>115 (66.9)</td>
<td>130 (73.9)</td>
</tr>
<tr>
<td>Type of pneumonia, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare-associated</td>
<td>26 (15.1)</td>
<td>30 (17.1)</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>146 (84.9)</td>
<td>146 (83.0)</td>
</tr>
<tr>
<td>Ventilator-associated</td>
<td>104 (60.5)</td>
<td>117 (66.5)</td>
</tr>
<tr>
<td>Bacteremia, No. (%)</td>
<td>9 (5.2)</td>
<td>20 (10.8)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.2 (6.4)</td>
<td>17.4 (6.0)</td>
</tr>
<tr>
<td>Modified CPIS (maximal score 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.7 (2.1)</td>
<td>9.4 (2.3)</td>
</tr>
<tr>
<td>Vancomycin serum trough levels, median (interquartile range) µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3 (n=140)</td>
<td>12.3 (9.45)</td>
<td></td>
</tr>
<tr>
<td>Day 6 (n = 90)</td>
<td>14.7 (10.40)</td>
<td></td>
</tr>
<tr>
<td>Day 9 (n = 33)</td>
<td>16.1 (11.30)</td>
<td></td>
</tr>
</tbody>
</table>

RETURN TO ‘PRE’-CLINICAL DATA
### Mechanism Realized

- Vancomycin appears to induce oxidative stress at the renal proximal tubule; free radical scavenging and antioxidant molecules have minimized this toxicity.

**Figure.** A biopsy showing tubular damage secondary to vancomycin toxicity at the location immediately above the asterix *. Some of tubules contain hyaline or epithelial casts in their lumina (*A), show vacuolization of their cytoplasm (*B), display moderate acute tubular necrosis (*C), and in one case a glomerular afferent arteriole shows swollen endothelia and an occlusive change (*D).

2. Scheetz M, currently unpublished.
Ability to detect kidney injury according to time and method of detection

A. Point of hypothesized detection of novel biomarker abnormality
B. Point of irreversible nephrotoxic event
C. Point at which nephrotoxicity is detected with standard clinical variables
Kidney Biomarkers

PSTC Nephrotoxicity Working Group...
ideal renal safety biomarker:
• Kidney injury identified early
• Dose response relationship with toxicity
• Applicable to various species, including humans
• Specific to kidney injury
• Is a barometer of progression of injury and recovery from damage
• Limitations well characterized
• Can easily be measured in readily available body fluids or tissues (e.g. urine).

https://c-path.org/programs/pstc/pstc-tools/?anchor=section-572#section-572
KIM is Kidney specific

Bilateral Renal Ischemia/Reperfusion

Urinary KIM-1 by Dose and Days of Therapy

- Similar data have been shown by others\(^2\)

Same Vancomycin Dose x 7 days, Split v. Not

**Serum Creatinine**

- Control
- Vancomycin 400 mg/kg split BID
- Vancomycin 400 mg/kg QD

**BUN**

- Control
- Vancomycin 400 mg/kg split BID
- Vancomycin 400 mg/kg QD

Gaps in the Road

- Barriers to elucidating EXPOSURE response for vancomycin-associated AKI:
  - Additional covariates (e.g. severity of illness) may obscure exposure-response relationship
  - Homogeneity of current human dosing strategies

- Need for innovative approaches to detecting AKI:
  - Use of novel urinary biomarkers may enhance detection of AKI prior to histopathological change
  - Combining animal models and novel biomarkers allows establishment of causative relationship
Our Group: Intraperitoneal Dosing, Vancomycin in SD Rats

Data from: Rhodes, Scheetz, et al.
AAC Accepted Manuscript Posted Online 18 July 2016
Kidney Injury Molecule 1 vs. Vancomycin PK Parameters:
24-hour dosed animals only

Scheetz et al. not yet published. NIAID R15AI105742
Viewed via Stratifications

Scheetz et al. not yet published.
MINIMIZATION OF TOXICITY?
GUIDED STRATEGIES.
Continuous Infusion vs. Intermittent Infusion

- Update of: Cataldo MA, et al. JAC 2012
  - Specific to Nephrotoxicity and additional studies included..

Data abstracted from: Hanrahan TP, Roberts J, et al. IJAA, 2015
So what was going on with that ‘odd ball’?

1430 patients included; those with central lines received CI per hospital protocol

Summary of Patients Data Receiving Vancomycin by Infusion Method Type

<table>
<thead>
<tr>
<th>Percent (%)</th>
<th>Continuous Infusion (n = 653)</th>
<th>Intermittent Infusion (n = 390)</th>
<th>Mixed (n = 221)</th>
<th>Unknown (n = 166)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median serum vancomycin concentration (mg/L), median (IQR)</td>
<td>18.4 (15.6-21.2)</td>
<td>8.8 (6.5-11.2)</td>
<td>15.5 (12.1-19.1)</td>
<td>11.9 (8.2-17.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Average vanco g/day, median (IQR)</td>
<td>1.7 (1.2-2.1)</td>
<td>1.5 (0.9-2.2)</td>
<td>1.7 (1.2-2.1)</td>
<td>2.0 (1.0-2.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Length of vancomycin therapy (d), median (IQR)</td>
<td>5.3 (3.4-10.3)</td>
<td>4.4 (2.5-7.3)</td>
<td>5.0 (2.9-9.2)</td>
<td>0.8 (0.4-1.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>172 (26.3)</td>
<td>49 (12.6)</td>
<td>31 (14.0)</td>
<td>36 (21.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>161 (24.7)</td>
<td>77 (19.7)</td>
<td>44 (19.9)</td>
<td>18 (10.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Intermittent Infusion is associated with OR=8.2, p<0.001 risk of nephrotoxicity after controlling for vasopressors, duration of therapy, and interaction between serum concentrations and infusion scheme.

So Let’s Say it is AUC…

What does this mean for our patients?

High variability with standard dosing!

Vancomycin exposures of simulated profiles with two doses given by 1-h intravenous infusion every 12h

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value achieved with dose of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1000 mg</td>
</tr>
<tr>
<td>Median (range) AUC$_{0-24}$ (mg·h/liter)</td>
<td>343.1 (72.5-2194.0)</td>
</tr>
<tr>
<td>% (no.) of patients with AUC$_{0-24}$ (mg·h/liter)</td>
<td></td>
</tr>
<tr>
<td>≥ 400</td>
<td>28.7 (1435)</td>
</tr>
<tr>
<td>≥ 700</td>
<td>2.7 (136)</td>
</tr>
<tr>
<td>≥ 1300</td>
<td>0.02 (1)</td>
</tr>
<tr>
<td>Median (range) AUC$_{0-24}$ of those with trough concn &gt;20 mg/liter</td>
<td>602.0 (225.7-2194.0)</td>
</tr>
<tr>
<td>% (no.) with trough concn of &gt;20 mg/liter and AUC$_{0-24}$ (mg·h/liter) of:</td>
<td></td>
</tr>
<tr>
<td>&lt; 400</td>
<td>14 (52)</td>
</tr>
<tr>
<td>400-700</td>
<td>61 (229)</td>
</tr>
<tr>
<td>≥ 700</td>
<td>26 (97)</td>
</tr>
</tbody>
</table>

Though Bayesian ‘trough only’ does well... with a few exceptions. Otherwise, use at least 2 levels.
What is the magic AUC?

• Retrospective, single-center, observational cohort study from 2014 to 2015 at the Detroit Medical Center

• Inclusion criteria: age ≥ 18 y; ≥ 72 h of intravenous vancomycin; ≥ 1 serum vancomycin concentration during initial 96 h; bacteremia indication per pharmacy to dose order

Zasowski, Murray, Trinh, Finch, Mynatt, Rybak. Microbe 2016
So Less can be More?

• Retrospective, multi-center, quasi-experimental study of patients in 2 treatment groups
  • Pre-intervention group (goal= Trough 15-20 mg/L goal)
  • Post-intervention group (goal= AUC$_{24h}$ 400-600 mg*hr / L)
  • Bayesian exposure profiles bacteremic patients (n=160), decreased vancomycin exposure for those under AUC strategy.

<table>
<thead>
<tr>
<th>Outcome (Matched Cohort) : Nephrotoxicity</th>
<th>Trough (n=548)</th>
<th>AUC (n=548)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AKIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>108 (19.7)</td>
<td>86 (15.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Stage 2</td>
<td>66 (12.0)</td>
<td>41 (7.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stage 3</td>
<td>18 (3.3)</td>
<td>12 (2.2)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>RIFLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>101 (18.4)</td>
<td>90 (16.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Injury</td>
<td>39 (7.1)</td>
<td>23 (4.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Failure</td>
<td>18 (3.3)</td>
<td>12 (2.2)</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Key Takeaways

- Key Takeaway #1
  - We learn more each day about Vancomycin induced Nephrotoxicity

- Key Takeaway #2
  - Troughs are not likely to predict Nephrotoxicity (other than after the fact or by using Bayesian modeling)

- Key Takeaway #3
  - AUC monitoring may be needed to prevent nephrotoxicity (while ensuring appropriate exposures for patients). Continuous infusion may be on the horizon.
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  - Cameron Cluff, PharmD candidate

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Vancomycin PK/PD Efficacy

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Disclosures

- All materials are the property of the authors, and may not be copied or used for commercial purposes without written permission from the owner.

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Methicillin Resistance among *S. aureus* Worldwide

- US: 34-59%
- Nigeria, Kenya: 34%
- Latin America: 35%
- South Africa: 43%
- Europe: 26%
- Japan: 72%
- Singapore: 62%
- Australia: 24%

References:

Methicillin Resistance among *S. aureus* Surveillance Data from 300 US Labs

- Population-based studies indicate that MRSA is not limited to intensive care settings.
- MRSA is now commonplace in the inpatient and outpatient settings.
- Epidemic strains of MRSA from the community have emerged as causes of hospital-acquired infections.

**MRSA Trends by Patient Location**

Empiric Treatment of Suspected *S. aureus* Infections

- Clinicians should consider MRSA as a potential pathogen in patients presenting with a clinical syndrome consistent with *S. aureus*
  - Endemic in healthcare institutions
    - Both intensive care unit (ICU) and non-ICU
  - Problematic in the community setting
- Important to get it right the first time

Centers for Disease Control and Prevention. National Nosocomial Infections Surveillance (NNIS) System
Delayed Therapy for *S. aureus* Bacteremia Increases Mortality and Length of Stay

*Breakpoint between early and delayed treatment was 44.75 hours.*

Vancomycin Utilization Over 20 Years

Vancomycin Susceptibility in *S. aureus*

- Over 20 million days of vancomycin therapy are used annually in the United States alone.\(^1\)

- Despite heavy reliance on vancomycin, MRSA infections are still nearly 100% susceptible to vancomycin as per Clinical Laboratory Standards Institute (CLSI) and FDA susceptibility breakpoints.\(^2,3\)

  - Antibiotic susceptibility is based on the minimum inhibitory concentration (MIC)
    - MIC: lowest or minimum antimicrobial concentration that inhibits visible microbial growth in artificial media after a fixed incubation time

---

**S. aureus Susceptibility Defined: Vancomycin Resistant (VRSA), Vancomycin Intermediate (VISA), Heteroresistance (hVISA)**

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>VRSA</th>
<th>VISA</th>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC ≥16 µg/mL†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–8 µg/mL†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC ≤2 µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *In addition to the MIC, hVISA strains are identified by population analysis profiling (PAP), simplified PAP by BHIA-V4, simplified PAP on Mueller-Hinton agar, Etest, Disk-agar, MicroScan, and resistant mutant emergence.
- †Breakpoints reflect 2006 CLSI guidelines.

### Lack of Vancomycin MIC Creep by Microbroth Dilution MIC Testing

<table>
<thead>
<tr>
<th>Organism, year</th>
<th>No. of isolates tested</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;, mg/L</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, mg/L</th>
<th>Percentage of isolates, according to MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>5966</td>
<td>1</td>
<td>1</td>
<td>5.3  0.1  0.0</td>
</tr>
<tr>
<td>1999</td>
<td>5011</td>
<td>1</td>
<td>1</td>
<td>4.8  &lt; 0.1  0.0</td>
</tr>
<tr>
<td>2000</td>
<td>6346</td>
<td>1</td>
<td>1</td>
<td>7.8  &lt; 0.1  &lt; 0.1</td>
</tr>
<tr>
<td>2001</td>
<td>5907</td>
<td>1</td>
<td>1</td>
<td>6.5  0.1  0.0</td>
</tr>
<tr>
<td>2002</td>
<td>7046</td>
<td>1</td>
<td>1</td>
<td>6.4  0.0  0.0</td>
</tr>
<tr>
<td>2003</td>
<td>5182</td>
<td>1</td>
<td>1</td>
<td>4.7  0.1  0.0</td>
</tr>
</tbody>
</table>


Clinical MRSA blood isolates collected at a single tertiary care center

# Relationship between vancomycin MIC and outcomes for serious MRSA infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Primary Outcome</th>
<th>MIC Testing Methodology</th>
<th>MIC Range (mg/L)</th>
<th>Low MIC Outcomes</th>
<th>High MIC Outcomes</th>
<th>Difference in Outcomes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maclayton et al.</td>
<td>Adult hemodialysis patients with MRSA bacteremia</td>
<td>Mortality</td>
<td>Vitek</td>
<td>≤ 0.5 (n=33) 2 (n=17)</td>
<td>24%</td>
<td>35%</td>
<td>11%</td>
<td>NS at &lt;0.05 &lt;0.001</td>
</tr>
<tr>
<td>Hidayat et al.</td>
<td>Adult patients with MRSA infection</td>
<td>Treatment Failure</td>
<td>Etest</td>
<td>≤ 1 (n=40) 2 (n=39)</td>
<td>15%</td>
<td>38%</td>
<td>23%</td>
<td>0.02</td>
</tr>
<tr>
<td>Soriano et al.</td>
<td>Adult patients with MRSA bacteremia</td>
<td>30-Day Mortality</td>
<td>Etest</td>
<td>1 (n=38) 1.5-2 (n=40)</td>
<td>15.8%</td>
<td>39.8%</td>
<td>24%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>Adult patients with MRSA infection</td>
<td>Treatment Failure</td>
<td>Etest</td>
<td>≤ 1 (n=38) &gt; 1 (n=45)</td>
<td>11%</td>
<td>38%</td>
<td>27%</td>
<td>0.034</td>
</tr>
<tr>
<td>Lodise et al.</td>
<td>Adult patients with MRSA bacteremia</td>
<td>Treatment Failure</td>
<td>Etest</td>
<td>&lt; 1.5 (n=26) ≥ 1.5 (n=66)</td>
<td>15.4%</td>
<td>36.4%</td>
<td>21%</td>
<td>0.049</td>
</tr>
<tr>
<td>Musta et al.</td>
<td>Adult patients with MRSA bacteremia</td>
<td>Mortality</td>
<td>Etest</td>
<td>≤ 1.5 (n=429) ≥ 2 (n=60)</td>
<td>25.7%</td>
<td>47.6%</td>
<td>21.9%</td>
<td>0.03</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Adult patients with MRSA bacteremia</td>
<td>30-Day Mortality</td>
<td>BMD</td>
<td>= 2 (n=26) &lt; 2 (n=97)</td>
<td>27.8%</td>
<td>50%</td>
<td>22.2%</td>
<td>0.057</td>
</tr>
</tbody>
</table>

AJHP 2009 Consensus Review on the Therapeutic Monitoring of Vancomycin

- The AUC/MIC is the pharmacodynamic parameter best associated with vancomycin efficacy against *Staphylococcus aureus*.
- An AUC/MIC ratio of 400 has been advocated as a target to achieve clinical effectiveness with vancomycin
  - An AUC/MIC ratio of 400 is unachievable with conventional dosing in patients if MIC is $\geq 2$ mg/L.
- Total troughs serum vancomycin concentrations of 15-20 mg/L are recommended for complicated infections.
  - AUCs are not determined in clinical practice due to the perceived difficulty in calculating AUC/MIC values.

Pharmacodynamic Indices and \textit{in-vitro} Activity for Vancomycin: Murine Thigh Infection Model

Inoculum Effect of Vancomycin with *Staphylococcus aureus* in neutropenic mice at $10^5$ and $10^7$ CFU, opposite thighs

Changes of inoculum over 24 hours (log10 CFU/Thigh)

<table>
<thead>
<tr>
<th>log10 CFU/Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4</td>
</tr>
<tr>
<td>-3</td>
</tr>
<tr>
<td>-2</td>
</tr>
<tr>
<td>-1</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Dosage of Vancomycin (mg/kg/day)

In Vivo PD of Vancomycin against VSSA: Neutropenic Murine Thigh-Infection Model

Free drug $\text{AUC}_{0-24}/\text{MIC}$ for a Static Effect with Various Staphylococci

VSSA* 157-263

- $f\text{AUC}/\text{MIC}$ upwards of 400-500 were required for a 2-log reduction

Similar dose-response studies performed with 2 of 3 strains at a 1.0 to 1.3 log lower inoculum: 46-87% reduction in the magnitude of the static dose.

*Starting inoculum $10^{6.1-6.9}$ CFU/thigh

Vancomycin PK-PD Targets in in Vitro PD Model against MRSA*

<table>
<thead>
<tr>
<th>Model Fit Parameter</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect at 0 mg/L*h</td>
<td>2.28</td>
</tr>
<tr>
<td>Hills Constant (Slope)</td>
<td>2.81</td>
</tr>
<tr>
<td>Maximal Effect (Change from Control)</td>
<td>-2.77</td>
</tr>
</tbody>
</table>

**PK-PD TARGET**

<table>
<thead>
<tr>
<th>fAUC:MIC to achieve:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.5 Log₁₀ CFU/ml</td>
<td>113</td>
</tr>
<tr>
<td>-1.0 Log₁₀ CFU/ml</td>
<td>151</td>
</tr>
<tr>
<td>-1.5 Log₁₀ CFU/ml</td>
<td>260</td>
</tr>
<tr>
<td>-2.0 Log₁₀ CFU/ml</td>
<td>Not Achievable</td>
</tr>
<tr>
<td>-3.0 Log₁₀ CFU/ml</td>
<td>Not Achievable</td>
</tr>
</tbody>
</table>

*Two agr-functional, group II MRSA clinical isolates obtained from patients with a bloodstream infection (MIC 1.0 mg/liter) at a high inoculum of 10⁸ CFU/ml.

Vancomycin Pharmacodynamics in Patients with \textit{S. aureus} Pneumonia

\[ P = 0.0402 \]

Probability of AUC/MIC ratio ≥ 400 for vancomycin regimens of varying intensity when Cmin is between 15 and 20 mg/L

Among the 9,999 subjects simulated, the total number of subjects with Cmin values 15 – 20 mg/L were: a) 406 subjects (0.5G Q12h); b) 1100 subjects (1G Q12h); c) 1190 subjects (1.5G Q12h); d) 1096 subjects (2G Q12h)

Increasing the Dose of Vancomycin to Reach Higher Trough Levels May Not Improve Clinical Outcomes

Prospective Cohort Single-Center Study

Target vancomycin trough levels, 15 to 20 µg/mL

Relationship between Troughs and Outcomes: Invasive MRSA Infections

- The clinical benefits of maintaining higher vancomycin trough values have not been well described.\(^1\)-\(^7\)

- Link between clinical success and vancomycin trough values only observed in one study among MRSA bacteremic patients.\(^3\)
  - Failure among patients with troughs < 15 mg/L: 61%
  - Failure among patients with troughs between 15-20 mg/L: 40%
  - Failure rate among patients with trough > 20 mg/L: 50%

- A growing number of studies have found increased rates of acute kidney injury with the use of intensive vancomycin regimens aimed at achieving trough in excess of 15 mg/L.\(^8\)

Vancomycin-Induced Nephrotoxicity

In the “15-20 mg/L” Trough Era: A Systematic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Troughs &gt; 15 mg/L</th>
<th>Troughs &lt; 15 mg/L</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso et al (3)</td>
<td>42/142</td>
<td>13/146</td>
<td>10.7%</td>
<td>4.30 [2.19, 8.43]</td>
</tr>
<tr>
<td>Cano et al (4)</td>
<td>22/89</td>
<td>7/99</td>
<td>8.1</td>
<td>4.32 [1.74, 10.69]</td>
</tr>
<tr>
<td>Chung et al (7)</td>
<td>12/25</td>
<td>16/48</td>
<td>7.4</td>
<td>1.85 [0.69, 4.96]</td>
</tr>
<tr>
<td>Hermsen et al (19)</td>
<td>5/16</td>
<td>4/39</td>
<td>4.3</td>
<td>3.98 [0.91, 17.46]</td>
</tr>
<tr>
<td>Hidayat et al (20)</td>
<td>11/63</td>
<td>0/32</td>
<td>1.4</td>
<td>14.24 [0.81, 249.87]</td>
</tr>
<tr>
<td>Jeffres et al (24)</td>
<td>27/49</td>
<td>13/45</td>
<td>8.6</td>
<td>3.02 [1.28, 7.11]</td>
</tr>
<tr>
<td>Kralovicova et al (26)</td>
<td>21/60</td>
<td>29/138</td>
<td>10.7</td>
<td>2.02 [1.04, 3.96]</td>
</tr>
<tr>
<td>Kullar et al (27)</td>
<td>27/139</td>
<td>23/141</td>
<td>11.5</td>
<td>1.24 [0.67, 2.28]</td>
</tr>
<tr>
<td>Kullar et al (28)</td>
<td>8/116</td>
<td>1/84</td>
<td>2.4</td>
<td>6.15 [0.75, 50.13]</td>
</tr>
<tr>
<td>Lodise et al (36)</td>
<td>7/27</td>
<td>14/139</td>
<td>7.1</td>
<td>3.13 [1.12, 8.69]</td>
</tr>
<tr>
<td>McKamy et al (38)</td>
<td>16/57</td>
<td>8/110</td>
<td>8.0</td>
<td>4.98 [1.98, 12.52]</td>
</tr>
<tr>
<td>Minejima et al (40)</td>
<td>17/72</td>
<td>25/155</td>
<td>10.5</td>
<td>1.61 [0.80, 3.21]</td>
</tr>
<tr>
<td>Prabaker et al (49)</td>
<td>7/54</td>
<td>24/294</td>
<td>8.2</td>
<td>1.68 [0.68, 4.11]</td>
</tr>
<tr>
<td>Zimmerman et al (63)</td>
<td>8/12</td>
<td>0/33</td>
<td>11.3</td>
<td>126.56 [6.19, 2585.90]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>921/1,503</td>
<td></td>
<td>100.0%</td>
<td>2.76 [1.94, 3.93]</td>
</tr>
</tbody>
</table>

Total events 230/177

Heterogeneity: Tau² = 0.18; Chi² = 23.80, df = 13 (P = 0.03); I² = 45%

Test for overall effect: Z = 5.66 (P < 0.00001)
Relationship between the Vancomycin Trough Value and AUC_{0-24}hours

Limited Data in Support of AUC/MIC ratio of ≥ 400

- Data, albeit limited, from the neutropenic mouse thigh infection model indicate that the bactericidal activity of vancomycin is maximized when AUC/MIC > 400.\(^1\)
  - It is unclear if data from this pre-clinical infection model is predictive of patient outcomes for bloodstream infections.
- Limited clinical data in support of the AUC/MIC ratio > 400 target among patients with invasive infections due to MRSA.\(^2-4\)
- Importantly, most published vancomycin exposure-response clinical evaluations\(^2-4\) used a simple formula based on total daily vancomycin dose and estimated renal function to estimate the AUC.
  - It is nearly impossible to generate valid estimates of exposure variables in a given individual based on glomerular filtration estimation formulas alone due to the presence of wide inter-patient exposure variability.

Effect of the Vancomycin Exposure Profile on the Outcomes of Patients with MRSA Bloodstream Infections

- Using a validated Bayesian method to estimate the vancomycin exposure profile with limited vancomycin blood concentration data¹, Lodise and colleagues evaluated the relationship between vancomycin exposure and failure among a retrospective cohort of hospitalized, adult patients with MRSA bloodstream infections at an academic medical center.²
- Given the time-critical nature of the first 48 treatment hours for MRSA bloodstream infections³, they assessed the relationships between day 1 and day 2 vancomycin exposure variables (Cmin/AUC and AUC/MIC) and failure.
  - Considered both broth micro-dilution MICs and ETEST™ MICs
  - Failure defined as any one of the following: 30-day mortality, bacteremia > 7 days, or recurrence <60 days of completing therapy

Observed vs. Predicted Plots for MAP-Bayesian and Formula-Based Estimation Approaches

MAP-Bayesian Approach

Formula-Based Approach

Bivariate Rel. CART-Derived Day 1 and Day 2 AUC/MIC Exposures and Failure

AUC/MIC\textsubscript{BMD} ≥ CART breakpoint

AUC/MIC\textsubscript{ETEST} ≥ CART breakpoint

RR = 0.6, 95% CI: 0.3-0.9

## Rel. between CART-Derived AUC Exposure Variables and Outcomes: Poisson Regression

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Overall Failure*</th>
<th>30-Day Mortality**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{0-24hr}/\text{MIC}_{BMD} \geq 521)</td>
<td>0.54</td>
<td>0.32-0.91</td>
</tr>
<tr>
<td>(AUC_{0-24hr}/\text{MIC}_{ETEST} \geq 303)</td>
<td>0.48</td>
<td>0.29-0.78</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{24-48hr}/\text{MIC}_{BMD} \geq 650)</td>
<td>0.58</td>
<td>0.34-0.99</td>
</tr>
<tr>
<td>(AUC_{24-48hr}/\text{MIC}_{ETEST} &gt; 320)</td>
<td>0.53</td>
<td>0.32-0.88</td>
</tr>
</tbody>
</table>

*All variables associated with failure at \(P \leq 0.2\) and considered at model entry included: \(P\)-value \(\leq 0.2\) included: APACHE-II score, chronic obstructive pulmonary disease, diabetes mellitus, malignancy, recent prior surgery, MIC\(ETEST \geq 1.5\) mg/L, and cumulative number of reduced vancomycin susceptibility phenotypes.

**Baseline covariates associated with 30-day mortality at \(P \leq 0.2\) and considered at model entry included: Baseline covariates associated with 30-day mortality at a \(P\)-value \(\leq 0.2\) included: APACHE-II Score, malignancy, MIC\(ETEST \geq 1.5\) mg/L, MIC\(BMD \geq 1\) mg/L, and MBC/MIC ratio > 4.

The Association between the Vancomycin Day 1 AUC and Outcomes Among Patients with MRSA Infective Endocarditis

Vanco PK/PD Targets from Clinical Evaluations using Bayesian AUC Estimation

- Brown, J. et al. AAC 2012
  - 50 Patients with MRSA IE/attributable mortality
    - AUC/MIC\(_{\text{Etest}}\) at steady state > 211 – Bayesian???

  - 76 patients with MRSA bacteremia/30 day all cause mortality
    - AUC/MIC\(_{\text{BMD}}\) at steady state > 430 – Bayesian
    - AUC/MIC\(_{\text{Etest}}\) at steady state > 385

  - 117 patients with MRSA bacteremia – composite – clearance, mortality, >7 days BS
    - AUC/MIC\(_{\text{BMD}}\) at steady state > 392.7 – Bayesian
    - AUC/MIC\(_{\text{Etest}}\) at steady state > 397.2

  - 59 patients with MRSA bacteremia and MRSA osteomyelitis–time to microbiologic clearance
    - AUC/MIC\(_{\text{Etest}}\) at steady state > 293 – Bayesian
Bayesian and Equation-Based Approaches to Estimating the AUC

Bayesian Approach to AUC Estimation

- Bayesian software only requires four specific components
  - Structural mathematical model that best describes the pharmacokinetics (PKs) of a given agent
  - Density file, which contains the parameter estimates and their associated dispersion for the embedded structural PK model (Bayesian prior)
  - Patient file that contains their drug dosing and collected PK data
  - Patient “target” file which contains the target exposure profile and initial estimates of future dosing regimens

- With this information, the Bayesian dose optimization software calculates a Bayesian posterior parameter value file or that patient.
  - The dose optimization software then calculates the optimal dosing regimen based on the specified exposure profile in the target file
Advantages of Bayesian Approach to AUC Estimation

- Only requires trough data to accurately estimate the AUC.
- Innovative treatment schemas, such as front-loading doses with a transition to a lower maintenance dosing regimen, can be designed to rapidly achieve target concentrations within the first 24 to 48 hours among critically ill patients.
- Concentration-time information does not need to be collected at “steady-state” (after the 3rd or 4th dose).
- Ability to include covariates, such as $\text{CL}_{\text{CR}}$, in the structural PK models (Bayesian prior density file) that account for the pathophysiological changes that readily occur in critically ill patients.

Equation-Based Approach to AUC Estimation

- Use of a post-distributional peak (1-2 hours post infusion) and trough concentrations can inform the daily AUC value with reasonable precision and low bias with simple first-order PK formulas.

- Simple to use and can be programmed into electronic medical system to automatically compute the AUC.

- Disadvantages
  - Highly preferably to have concentration time data over same dosing interval (peak and trough data).
  - Can only provide a snapshot of the AUC for the sampling period.
  - May provide unreliable estimates when drug is not near steady-state conditions.
The theoretical concentration at the end of infusion is given by the following equation:

\[ AUC_{t0-t2} = \frac{t' \times (Ceoi' + Ct)}{2} + \frac{Ceoi' - Ct}{Ke} \]

Vancomycin Concentration (mg/L)

Time (hours)

AUC_{t0-t2} = \frac{C_{s0} - C_t}{Ke}

Expected Profile

Mono-exponential fit

peak

trough

Valid Estimation of Vancomycin AUC with Trough-only Data using Bayesian Est. Software

<table>
<thead>
<tr>
<th>AUC Estimation Method</th>
<th>Number of Samples</th>
<th>AUC (mg*h/L)</th>
<th>Ratio of computed AUC to reference</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayesian</td>
<td>All</td>
<td>250 [84.1, 688]</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Bayesian</td>
<td>Trough only</td>
<td>259 [82.9, 573]</td>
<td>1.0 [0.74, 1.28]</td>
<td>0.948</td>
</tr>
<tr>
<td>Equation-based method 1</td>
<td>Peak and Trough</td>
<td>239 [90.6, 662]</td>
<td>0.99 [0.83, 1.16]</td>
<td>0.971</td>
</tr>
<tr>
<td>Equation-based method 2</td>
<td>Peak and Trough</td>
<td>247 [100, 675]</td>
<td>1.02 [0.85, 1.22]</td>
<td>0.987</td>
</tr>
</tbody>
</table>

Summary

- Further studies are needed to determine if optimization of vancomycin therapy can improve outcomes without subjecting patients to an increased risk of vancomycin-related toxicities
  - Must determine PK/PD targets for efficacy and toxicity to truly optimize vancomycin dosing and evaluate its PK/PD profile
- Drug entities that exploit new targets are available
- Our challenge is to appropriately place these new antimicrobials in roles that are suitable to optimize strengths, minimize weaknesses, and (hopefully) prevent emergence of resistance
Section End
Vancomycin is Clinically Dead

Michael J. Rybak, Pharm.D.,Ph.D.
Professor of Pharmacy,
Department of Pharmacy Practice,
Adjunct Professor of Medicine,
Division of Infectious Diseases
Wayne State University
Detroit, Michigan
Disclosures/Acknowledgments

- Currently receiving grant support, serve as a speaker or consultant for the following:
  - Accelerated Diagnostics
  - Allergan
  - Bayer
  - Cempra
  - Melinta
  - Merck
  - The Medicine Company
  - National Institutes of Health
    - R21 AI109266-01 (PI)
    - R01 AI121400-01 (PI)
    - Contract: HHSN22201000039C (Co-Inv)
  - Theravance
1956: Screened for activity from soil sample obtained from Borneo

Derived from *Streptomyces orientalis*

Compound #05865 named vancomycin (derived from “vanquish”)

Approved by FDA for clinical use in 1958

- Limited clinical data

“Older than DIRT”

“Dubbed Mississippi Mud”
Vancomycin Historical Information

- Late 1950’s-60: Broad use initially due to lack of effective therapy
- 1960’s: Use decreased dramatically as semisynthetic penicillins became available and concerns over toxicity.
- 1970’s-90’s: Increased use due to increase in methicillin-resistant *S. aureus*
METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

80,461 SEVERE MRSA INFECTIONS PER YEAR
11,285 DEATHS FROM MRSA PER YEAR

STAPH BACTERIA ARE A LEADING CAUSE OF HEALTHCARE-ASSOCIATED INFECTIONS

MIDYEAR
2016
Clinical Meeting & Exhibition

Vancomycin has been the Mainstay of Therapy for MRSA but it has Major Issues

<table>
<thead>
<tr>
<th>MIC, µg/ml</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>≥32</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSSA</td>
<td></td>
<td></td>
<td>hVISA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- The FDA revised vancomycin breakpoints in line with the CLSI

1. CLSI. Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. M100-S18, 2008
hVISA and Clinical Failure

- Low level resistance MIC = 0.5-2 mg/L
- Subpopulation analysis demonstrate
  - Growth on BHI agar 4-6 mg/L of vanco
  - Additional applied vancomycin pressure can increase the MIC further
- Not screened for by clinical laboratories
- hVISA associated with prolonged bloodstream infections & clinical failure
- Estimates rates of hVISA: 5-50.7%

Clinical Outcomes in Patients with hVISA Bloodstream Infections

Logistic regression analysis of risk factors associated with vancomycin treatment failure

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hVISA</td>
<td>11.14 (4.32-28.74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>4.51 (1.75-11.60)</td>
<td>0.002</td>
</tr>
<tr>
<td>High-risk Infection*</td>
<td>2.53 (1.00-6.39)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Infection caused by infective endocarditis, pneumonia or bone & joint infection

Heteroresistance with Vancomycin in *S. aureus* is Seen with MICs as low as 1.0 µg/ml

Adapted from: Tenover FC, Moellering RC. *Clin Infect Dis*. 2007;44:1208-1215.
Etest MIC Distribution and hVISA

![Bar chart showing MIC distribution and hVISA](image)

- **n = 128**

hVISA and Vancomycin Exposure

**hVISA & Vancomycin**

### The Inoculum Impact
- Evaluated inoculum & impact of dose on vancomycin killing activity vs. hVISA
- Results:
  - Both hVISA & inoculum had a severe impact on vancomycin activity

---

Fifteen Percent of Wildtype MRSA are Tolerant to Vancomycin

- 74% of hVISA isolates are tolerant to vancomycin

Correlation of Vancomycin MIC and Patient Outcome
Therapeutic Efficacy of Vancomycin in Relation to MIC or Bactericidal Activity

Adapted from Sakoulas et al. 2004 J. Clin Microbiol. 42:2398-2402
Vancomycin MIC as a predictor for mortality in MRSA

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Risk of mortality (OR [95% CI])</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin MIC=1 μg/ml*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vancomycin MIC=1.5 μg/ml*</td>
<td>2.86 (0.87, 9.35)</td>
<td>0.08</td>
</tr>
<tr>
<td>Vancomycin MIC=2 μg/ml*</td>
<td>6.39 (1.68, 24.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inappropriate therapy†</td>
<td>3.62 (1.20, 10.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*MIC of vancomycin for first MRSA isolate determined by E-test
†Inappropriate therapy defined as empirical therapy to which the MRSA strain was resistant

# Vancomycin MIC as a predictor for treatment failure in MRSA infections

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>High MIC ≥1.5 µg/mL</th>
<th>Low MIC &lt;1.5 µg/mL</th>
<th>Weight</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bae et al.</td>
<td>14/37</td>
<td>12/28</td>
<td>10.9%</td>
<td></td>
</tr>
<tr>
<td>Choi et al.</td>
<td>12/34</td>
<td>10/36</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>Ferry et al.</td>
<td>9/24</td>
<td>10/36</td>
<td>9.7%</td>
<td></td>
</tr>
<tr>
<td>Hidayat et al.</td>
<td>20/51</td>
<td>9/28</td>
<td>11.0%</td>
<td></td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>17/45</td>
<td>4/38</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Lalueza et al.</td>
<td>3/13</td>
<td>17/50</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td>Lodise et al.</td>
<td>6/66</td>
<td>0/26</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>Moise et al.</td>
<td>11/14</td>
<td>5/20</td>
<td>6.0%</td>
<td></td>
</tr>
<tr>
<td>Moise-Broder et al.</td>
<td>23/25</td>
<td>22/38</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Takesue et al.</td>
<td>34/97</td>
<td>85/662</td>
<td>15.9%</td>
<td></td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>14/18</td>
<td>17/45</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>424/1015</strong></td>
<td></td>
<td><strong>100%</strong></td>
<td><strong>OR 2.69 (1.60, 4.51)</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>163</td>
<td>188</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.38; \chi^2 = 22.59, \text{df} 10 (P = 0.01); I^2 = 56\%$. Test for overall effect: $Z = 3.75 (P = 0.0002)$
Management of Vancomycin Failure

Consider change in therapy if:

1. Unsatisfactory clinical response, regardless of MIC or
2. Vanco MIC = 2 mg/L

No change in therapy if:

1. Clinically responding and
2. Vanco MIC < 2 mg/L

Day of vancomycin therapy

Avoiding the Perfect Storm: The Biologic and Clinical Case for Reevaluating the 7-Day Expectation for Methicillin-Resistant Staphylococcus aureus Bacteremia Before Switching Therapy

Ravina Kullar, James A. McKinnell, and George Sakoulas

1Department of Medical Affairs, Cubist Pharmaceuticals, Lexington, Massachusetts; 2Infectious Disease Clinical Outcomes Unit (ID-CORE), Los Angeles Biomedical Research Institute, David Geffen School of Medicine, University of California, 3Department of Medicine, Torrance Memorial Medical Center, and 4Division of Pediatric Pharmacology and Drug Discovery, University of California San Diego School of Medicine, La Jolla

Ineffective Vancomycin Therapy Negatively Impacts the Innate Immune System Response

**Figure 1.** Examples of cationic antimicrobial host defense peptides. Abbreviations: hBD-1, human beta-defensin-1; hNP-1, human neutrophil peptide-1; mprF, multiple peptide resistance factor; tPMP, thrombin-induced platelet microbicidal protein.

Ineffective Vancomycin → Cationic Peptide Resistance → Daptomycin Resistance

Alternative Therapy to Vancomycin for MRSA

- Ceftaroline
  - Bactericidal
  - Twice-daily administration

- Daptomycin
  - Conc-dependent killing
  - Bactericidal
  - Once-daily administration

- Linezolid
  - Bacteriostatic
  - Twice-daily administration

- Telavancin
  - Conc-dependent killing
  - Bactericidal
  - Once-daily administration

- Dalbavancin
  - Conc-dependent killing
  - Bactericidal
  - 1st and 8th day (ABSSSI)

- Oritavancin
  - Conc-dependent killing
  - Bactericidal
  - Single-dose (ABSSSI)

- Tedizolid
  - Bacteriostatic
  - Once-daily (ABSSSI)

Relationship Between Vancomycin Resistance and Daptomycin Susceptibility

- Correlation between reduced daptomycin susceptibility and vancomycin–intermediate *S aureus*\(^1\)

- Induction of daptomycin heterogeneous susceptibility in *S aureus* by exposure to vancomycin\(^2\)

- An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *S aureus*\(^3\)

- Association with prior vancomycin exposure and daptomycin non–susceptibility\(^4\)

---

Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant Staphylococcus aureus Bacteremia With Vancomycin Minimum Inhibitory Concentration >1 mg/L: A Matched Cohort Study

Kyle P. Murray,¹ Jing J. Zhao,¹ Susan L. Davis,³ Ravina Kullar,³ Keith S. Kaye,² Paul Lephart,⁴ and Michael J. Rybak¹,²,³

¹Department of Pharmacy, Detroit Medical Center, ²Division of Internal Medicine, Division of Infectious Diseases, Wayne State University and Detroit Medical Center, ³Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, and ⁴University Laboratories, Detroit Medical Center, Detroit, Michigan

# Predictors of Clinical Failure

## Multivariate Logistic Regression

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR</th>
<th>P</th>
<th>Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>4.4 (2.2-8.9)</td>
<td>&lt;0.001</td>
<td>5.8 (2.7-12.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vancomycin treatment</td>
<td>3.7 (1.9-7.4)</td>
<td>&lt;0.001</td>
<td>4.5 (2.1-9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>2.8 (1.4-5.4)</td>
<td>0.002</td>
<td>3.0 (1.4-6.3)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Variables with $P < 0.2$ when compared between treatment groups, and variables associated with clinical failure ($P < 0.2$) considered for inclusion.

Survival to 90 Days

Cox Proportional Hazards

$n = 170$

Predictors of mortality:
- Treatment with vancomycin*
- Malignancy
- Stroke/TIA
- ICU admission
- Decreased creatinine clearance

Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of MRSA Bacteremia

## Safety

<table>
<thead>
<tr>
<th></th>
<th>Daptomycin (n = 85)</th>
<th>Vancomycin (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity(^a)</td>
<td>0.00</td>
<td>22 (25.9%)</td>
</tr>
<tr>
<td>CPK elevation(^b)</td>
<td>1 (1.2%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Emergence of resistance</td>
<td>2 (2.4%)</td>
<td>0.00</td>
</tr>
<tr>
<td>during treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are no. (%) of patients.

a.  Nephrotoxicity defined as increase in SCr of ≥ 0.5 mg/dL or 50% over baseline on at least 2 consecutive occasions.

b.  Significant CPK elevation defined as increase > 5 ULN.

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

Michael J. Rybak,1,2,3 Ben M. Lomaestro,4 John C. Rotschafer,5 Robert C. Moeller, Jr.,6,7,8 Willam A. Craig,9 Marianne Billeter,10 Joseph R. Dalovisio,11 and Donald P. Levine9

1Anti-Infective Research Laboratory, Department of Pharmacy Practice, College of Pharmacy & Health Sciences, and 2Department of Medicine, School of Medicine, Wayne State University; and 3Detroit Receiving Hospital & University Health Center, Detroit, Michigan; 4Albany Medical Center, Albany, New York; 5Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis; 6Shields Warren-Mallinckrodt Medical Research, 7Harvard Medical School, and 8Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; 9University of Wisconsin School of Medicine and Public Health, Madison; and 10Ochsner Medical Centers and 11Department of Infectious Diseases, Ochsner Health System, New Orleans, Louisiana

Vancomycin Consensus Summary

- **PK/PD target is AUC/MIC**
  - Target AUC/MIC ≥ 400
    - Bacteremia
    - Pneumonia
    - Meningitis
    - Endocarditis
    - Osteomyelitis

- **Trough of 15-20 mg/L**
  - ≈ AUC/MIC of ≥400
    - Conc. < 10 mg/L encourages resistance

- Probability of achieving target AUC/MIC is 0% if vancomycin MIC = 2 µg/mL with low or high-dose vancomycin.
- Vanco MICs of 2 µg/mL associated with ↑ vanco Rx failures\(^1\)
- “MIC creep” observed in some centers but not others\(^2\):
  - Perhaps due to clonal dissemination or technical artifact.

Impact of Vancomycin Exposure on Outcomes of Patients with MRSA Bacteremia

Independent Predictors of Vancomycin Failure by Logistic Regression n= 320

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AOR; CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective endocarditis</td>
<td>4.55; 2.26-9.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nosocomial-acquired bacteremia</td>
<td>2.19; 1.21-3.97</td>
<td>0.009</td>
</tr>
<tr>
<td>Initial Vanco Trough Conc. &lt; 15 mg/L</td>
<td>2.0; 1.25-3.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Vanco MIC&gt; 1 mg/L by Etest</td>
<td>1.52; 1.09-2.49</td>
<td>0.045</td>
</tr>
</tbody>
</table>

* AUC_{24h} : MIC ratio <421 was significantly (P=0.038) associated with failure

Troughs > 15 are associated with Nephrotoxicity

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Tr&gt;15 mg/l</th>
<th>Total</th>
<th>Tr &lt; 15 mg/L</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio, CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso et al.</td>
<td>42</td>
<td>142</td>
<td>13</td>
<td>146</td>
<td>9.8%</td>
<td>4.3 (2.19-8.43)</td>
<td></td>
</tr>
<tr>
<td>Cano et al.</td>
<td>22</td>
<td>89</td>
<td>7</td>
<td>99</td>
<td>7.2%</td>
<td>4.32 (1.74-10.69)</td>
<td></td>
</tr>
<tr>
<td>Chung et al.</td>
<td>12</td>
<td>25</td>
<td>16</td>
<td>48</td>
<td>6.5%</td>
<td>1.85 (0.69-4.96)</td>
<td></td>
</tr>
<tr>
<td>Hermsen et al.</td>
<td>5</td>
<td>16</td>
<td>4</td>
<td>39</td>
<td>3.6%</td>
<td>3.98 (0.91-17.46)</td>
<td></td>
</tr>
<tr>
<td>Hidayat et al.</td>
<td>11</td>
<td>63</td>
<td>0</td>
<td>32</td>
<td>1.1%</td>
<td>14.24 (0.81-249.87)</td>
<td></td>
</tr>
<tr>
<td>Jeffres et al.</td>
<td>27</td>
<td>49</td>
<td>13</td>
<td>45</td>
<td>7.7%</td>
<td>3.02 (1.28-7.11)</td>
<td></td>
</tr>
<tr>
<td>Kralovicova et al.</td>
<td>21</td>
<td>60</td>
<td>29</td>
<td>138</td>
<td>9.8%</td>
<td>2.02 (1.04-3.96)</td>
<td></td>
</tr>
<tr>
<td>Kullar et al.</td>
<td>8</td>
<td>116</td>
<td>1</td>
<td>84</td>
<td>2.0%</td>
<td>6.15 (0.75-50.13)</td>
<td></td>
</tr>
<tr>
<td>Kullar et al.</td>
<td>27</td>
<td>139</td>
<td>23</td>
<td>141</td>
<td>10.6%</td>
<td>1.24 (0.67-2.28)</td>
<td></td>
</tr>
<tr>
<td>Lodise et al.</td>
<td>7</td>
<td>27</td>
<td>14</td>
<td>139</td>
<td>6.2%</td>
<td>3.13 (1.12-8.69)</td>
<td></td>
</tr>
<tr>
<td>McKamy et al.</td>
<td>16</td>
<td>57</td>
<td>8</td>
<td>110</td>
<td>7.0%</td>
<td>4.98 (1.98-12.52)</td>
<td></td>
</tr>
<tr>
<td>Minejima et al.</td>
<td>17</td>
<td>72</td>
<td>25</td>
<td>155</td>
<td>9.6%</td>
<td>1.61 (0.80-3.21)</td>
<td></td>
</tr>
<tr>
<td>Prabaker et al.</td>
<td>7</td>
<td>54</td>
<td>24</td>
<td>294</td>
<td>7.3%</td>
<td>1.68 (0.68-4.11)</td>
<td></td>
</tr>
<tr>
<td>Wunderink et al.</td>
<td>26</td>
<td>118</td>
<td>24</td>
<td>215</td>
<td>10.7%</td>
<td>2.25 (1.22-4.13)</td>
<td></td>
</tr>
<tr>
<td>Zimmermann et al.</td>
<td>8</td>
<td>12</td>
<td>0</td>
<td>33</td>
<td>1.0%</td>
<td>126.56 (6.19-2585.9)</td>
<td></td>
</tr>
</tbody>
</table>

Total events = 256

Vancomycin Toxicity Issues

- Infusion related (based on concentration)
  - Phlebitis
  - Red Man Syndrome

- Nephrotoxicity
  - Low (5-7%) at conventional doses (approximately 2 g/day)
  - Higher rates: up to 35% in combination with aminoglycoside
  - Limited data on doses at >4 g/day
    - Studies suggest rates of 13-34.6%

- Ototoxicity
  - Low incidence reported in the literature
  - Not demonstrated in animal models at high dosages
    - Recent report on ototoxicity and higher dosages
      - Higher in older > 53 yrs, long exposure (≈ 28 days)
      - And with higher troughs (mean 19 mg/L; P<0.008)

Probability of Remaining Non-Nephrotoxic

Stratum 0, linezolid

Stratum 1, standard-dose vancomycin (<4 g/day)

Stratum 2, high-dose vancomycin (≥4 g/day)

P < .0001

Days After Initiation of Therapy

**Initial Vancomycin Trough Concentration Detroit Medical Center**

<table>
<thead>
<tr>
<th>Total (N)</th>
<th>Missing</th>
<th>Unique</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>StDev</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>472</td>
<td>0 (0%)</td>
<td>227</td>
<td>4.70</td>
<td>64.80</td>
<td>18.25</td>
<td>7.96</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>.05</td>
</tr>
<tr>
<td>7.60</td>
</tr>
</tbody>
</table>

**Lowest values:** 4.7, 5.1, 5.3, 5.5, 5.5  
**Highest values:** 42.5, 42.7, 53.8, 61.4, 64.8

Data from the Detroit Medical Center 2014-15
Initial Vancomycin Trough Concentration 15-20 mg/l within 1st 72 hours Detroit Medical Center

15-20mg/L within 72 hours: Refresh Plot | View as Bar Chart

<table>
<thead>
<tr>
<th>Total (N)</th>
<th>Missing</th>
<th>Unique</th>
</tr>
</thead>
<tbody>
<tr>
<td>472</td>
<td>0 (0%)</td>
<td>2</td>
</tr>
</tbody>
</table>

Counts/frequency: Yes (142, 30.1%), No (330, 69.9%)

Data from the Detroit Medical Center 2014-15
Vancomycin Summary & Take Away

- Old and overused antibiotic
- Significant dose dependent nephrotoxicity
- High Association with failure
  - Suboptimal therapy
  - Elevated MICs
  - Tolerance
  - hVISA/VISA/VRSA
- Requires serum concentration monitoring
  - Target attainment highly variable
- Alternatives
  - Newer, safer & more potent

Optimization of vancomycin may improve patient outcomes; however:
- Difficult to achieve PK/PD target with MIC > 1 mg/L
- Associated with higher rates of nephrotoxicity
- Determination of the AUC may lower doses
- AUC/MIC targets for individual infections are needed
Section End
Vancomycin is clinically alive and well

Manjunath (Amit) P. Pai, PharmD
Associate Professor of Pharmacy
University of Michigan
A 45 y/o male presents with **fever** and **extensive cellulitis** of the right foot, having **failed** outpatient therapy with oral **clindamycin**. He is **allergic to penicillin** (hives). H/o diabetes and hypertension. Preliminary results from a culture of the **wound drainage** is **Gram positive cocci in clusters**. Which of the following agents would you use empirically?

- **A** Dalbavancin
- **B** Linezolid
- **C** Daptomycin
- **D** Vancomycin
The numbers favor....
Annual Number of Publications

Number of Publications per Year

Year

1960 1980 2000 2020

Vancomycin 4,000,000
Linezolid 2,000,000
Daptomycin 500,000

Google
2011 Market Share US ($)
Vancomycin 82% 200 M
Linezolid 10% 600 M
Daptomycin 8% 700 M

Substitution of Vancomycin would have cost ~$8.7 Billion
How many manufacturers of vancomycin have been approved by the US FDA:

A. 1 to 3
B. 3 to 6
C. 6 to 9
D. >10
# US FDA Approved Manufacturers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vancomycin</strong>*</td>
<td>Fresenis Kabi USA, Hospira, Mylan labs, Amneal Pharms, Akorn, Strides Pharma, Watson Labs, Sandoz, Lupin, Xelia Pharmas APS, Sagent Pharms, Teva Pharms, Emcure Pharms, CFT Pharmas, Aurobindo Pharma</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>Teva, Myland, Glenmark, Gate, Roxane, Sandoz, Hetero, Amneal, Fresenius, Alembic, Hospira, Alkem, Aurobindo, Novel</td>
</tr>
<tr>
<td><strong>Daptomycin</strong></td>
<td>Hospira, Teva, Crane</td>
</tr>
<tr>
<td>Telavancin</td>
<td>Theravance Biopharma</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>Forest Laboratories (Allergan)</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>Cubist (Merck)</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>The Medicines Company</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>Durata (Allergan)</td>
</tr>
</tbody>
</table>

---

*August 8, 2016

- Hospira had vancomycin **on shortage due to increased demand**.
- Fresenius Kabi has vancomycin injection on shortage due to increased demand.
- Mylan Institutional has vancomycin injection available.
- Baxter is allocating vancomycin.
So many new alternatives. One of them has to be better, right?
## Tried and Tested

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval Date</th>
<th>Indications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vancomycin</strong></td>
<td>1958</td>
<td>“Initial therapy when MRSA suspected”, endocarditis (including prosthetic valve), “septicemia”, bone infections, surgical measures, Penicillin allergies, etc</td>
<td></td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>2000</td>
<td>CSSTI, CAP, Nosocomial pneumonia, VRE</td>
<td></td>
</tr>
<tr>
<td><strong>Daptomycin</strong></td>
<td>2003</td>
<td>CSSTI, Bacteremia (Right Sided endocarditis MSSA/MRSA)</td>
<td></td>
</tr>
<tr>
<td>Telavancin</td>
<td>2009</td>
<td>CSSTI</td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>2010</td>
<td>ABSSSI, CAP</td>
<td></td>
</tr>
<tr>
<td>Tedizolid</td>
<td>2014</td>
<td>ABSSSI</td>
<td></td>
</tr>
<tr>
<td>Oritavancin</td>
<td>2014</td>
<td>ABSSSI</td>
<td></td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>2014</td>
<td>ABSSSI</td>
<td></td>
</tr>
</tbody>
</table>

CSSTI, complicated skin and skin structure infections  
ABSSSI, acute bacterial skin and skin structure infections  
CAP, community acquired pneumonia
CSSTI/ABSSSI Studies

Randomized Control Trials
Corey GR, et al. *NEJM* 2014;370:2180-2190
Boucher HW, et al. *NEJM* 2014;370:2169-2179
A 45 y/o male presents with **extensive cellulitis** of the right foot appears to be resolving but determined to also have **bone involvement**. His foot undergoes debridement but the patient requires **an additional 4-6 weeks** of therapy. What therapy would you select/continue:

A. Oritavancin
B. Linezolid
C. Daptomycin
D. Vancomycin
Antimicrobial Selection

- **Vancomycin:** 292
- **Linezolid:** 118
- **Daptomycin:** 105
- **Clindamycin:** 77

**Vancomycin (“first-line”)**
Prosthetic joint infection, MRSA
Prosthetic joint infection, penicillin-resistant *Enterococcus*
Meningitis, MRSA, SSTI

**Acknowledged Role:**
- **Daptomycin:** Bacteremia
- **Linezolid:** Pneumonia
Differentiation

- **Method of delivery (IV/PO):** Linezolid has the edge
- **Frequency of delivery:** Daptomycin has the edge
- **Direct Cost:** Linezolid has the edge

**Safety:**
- Vancomycin (nephrotoxicity)
- Linezolid (Myelosuppression)
- Daptomycin (Evolved since approval)

**Therapeutic Drug Monitoring:** Do you think you picked the right dosage regimen?
Post-Marketing Safety
(MedWatch, Drugs@FDA.gov)

- **Daptomycin**
  - Multiple label changes related to safety
  - Hypersensitivity, DRESS
  - Eosinophilic pneumonia
  - *C. difficile*–associated diarrhea
  - Peripheral Neuropathy
  - Visual disturbances
  - Acute kidney injury

- **Linezolid**
  - Drug-Drug interactions, SSRIs, rifampin
  - Myelosuppression
  - Tooth and tongue discolorations

- **Vancomycin**
  - DRESS
  - Corn allergies
A 60 y/o male presents with fever and chills. Blood cultures are positive for MRSA. Vancomycin is initiated but then switched to daptomycin after 72 hours based on MIC results (vancomycin MIC is 2 mg/L). What dosage of daptomycin would you initiate empirically in this 80 kg patient with normal kidney function?

- A 320 mg (4 mg/kg/day)
- B 480 mg (6 mg/kg/day)
- C 640 mg (8 mg/kg/day)
- D 800 mg (10 mg/kg/day)
Why are some experts suggesting the need for higher doses of daptomycin?

- If higher doses are “better” then does that not imply that there is an exposure-response relationship?

- What are the risks for underexposure?

- What are the risks for overexposure?

- How do we ensure that we are achieving the right exposure?
Evaluation of Daptomycin Exposure and Efficacy and Safety Endpoints To Support Risk-versus-Benefit Considerations

Sujata M. Bhavnani, Paul G. Ambrose, Jeffrey P. Hammel, Christopher M. Rubino, George L. Drusano

Institute for Clinical Pharmacodynamics, Latham, New York, USA; Institute for Therapeutic Innovation, College of Medicine, University of Florida, Lake Nona, Florida, USA

TABLE 2 Multivariable logistic regression model for clinical success

<table>
<thead>
<tr>
<th>Variable and value</th>
<th>Parameter estimate (SE)</th>
<th>Odds ratio (95% CI)</th>
<th>Likelihood ratio P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLCR (ml/min/1.73 m²)</td>
<td>≤51.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.59 (1.18)</td>
<td>13.3 (1.32–135)</td>
</tr>
<tr>
<td></td>
<td>&gt;51.2 to ≤88.9</td>
<td>4.30 (1.35)</td>
<td>73.7 (5.21–1,042)</td>
</tr>
<tr>
<td></td>
<td>&gt;88.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC/MIC ratio</td>
<td>≤1.081&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>&gt;1.081 to ≤2.334&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.29 (0.94)</td>
<td>3.64 (0.57–23.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;2.337</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin concn (g/dl)</td>
<td>&lt;2.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.55 (0.78)</td>
<td>4.70 (1.02–21.5)</td>
</tr>
<tr>
<td></td>
<td>≥2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis category&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.85 (1.28)</td>
<td>6.34 (0.52–77.2)</td>
</tr>
<tr>
<td></td>
<td>2, 3, or 4</td>
<td>3.03 (1.48)</td>
<td>20.8 (1.14–378)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Represents the reference group.
<sup>b</sup> With a 100% observed response (8/8) in the group with AUC/MIC ratios of ≤1.081, no estimates relative to this group could be obtained with maximum likelihood estimation. NE, not estimated.
<sup>c</sup> Diagnosis category definitions are as follows: 1, left-sided endocarditis; 2, 3, or 4, complicated right-sided endocarditis, uncomplicated right-sided endocarditis, or complicated bacteremia, respectively; 5, uncomplicated bacteremia.
<sup>d</sup> CI, confidence interval.

AUC/MIC of 1800 Equates to AUC of 450-900 h*mg/L, i.e. 4-8 mg/kg
Therapeutic Drug Monitoring

- **Vancomycin**
  - Target trough $>10$ mg/L to prevent emergence of resistance
  - Target trough of 15-20 mg/L for certain serious infections
  - Using twice the dosage as we did 20 years ago

- **Daptomycin**
  - Not as predictable as you may think
  - Experts think we should use twice as much as we did 10 years ago
  - Why is there no need for therapeutic drug monitoring?

- **Linezolid**
  - High variability in PK profile
  - Emerging data to suggest that a trough 2-7 mg/L may be optimal
  - So why does one dose fit all?

Oxazolidinones and Thrombocytopenia

Global Antimicrobial Use

Antimicrobial Resistance

- **14 Cases of VRSA**
  - 8 from Southeast Michigan

- **8 cases** of LRSA in 77 patients with cystic fibrosis, multiple such cases reported by several groups

The Lancet Infectious Diseases 2014 14, 742-750 DOI: (10.1016/S1473-3099(14)70780-7)
Key Takeaways

- **Vancomycin is alive**
  - Scientific interest and use of vancomycin remains robust because of our empiric need (may change with better diagnostics)

- **Vancomycin is well**
  - Randomized clinical trials maintain non-inferiority

- **Vancomycin is not without flaws but**
  - Other agents have safety concerns as well
  - Therapeutic drug monitoring may be needed for other agents
  - Over/misuse and resistance is a **concerning threat** for all agents

“Vancomycin’s long reign as first-line therapy for serious MRSA infections may be in its twilight, but there is still no proven heir to the throne.”

-Holland and Fowler (J Infect Dis. 2011; 204(3): 329-331)
Section End
Rebutal

M. Rybak
Why Amit is Wrong?

- Regarding the argument that vancomycin is popular, has more publications or increasing in use:
  - Its use is high because MRSA is high
  - It is the cheapest MRSA drug $$$
  - It is unrestricted and now used for prophylaxis
  - It has more clinical experience (papers) because it was made 60 years ago. It is a very very old drug!!!
  - It never went through randomized clinical trials for it’s indications
    - It is likely that if assessed today, it may not be on the market
Why Amit is Wrong?

- The majority of clinical trials comparing vancomycin were non-inferiority studies
  - Powered to be equal and not superior!
- Skin and Soft Tissue Trials
  - Everything works
  - Includes surgical interventions
- Dapto vs. Vanco (vanco + aminoglycoside)
- Linezolid vs. Vanco
  - probably not the best comparator

# Dalbavancin bacteremia

- Open-label trial

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome Description</th>
<th>Dalbavancin Outcome</th>
<th>Vancomycin Outcome</th>
<th>Risk Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>Clinical success @TOC</td>
<td>87.0% (20/23)</td>
<td>50.0% (14/28)</td>
<td>37.0% (11.1-56.3%)</td>
</tr>
<tr>
<td>mITT</td>
<td>Micro success @TOC</td>
<td>95.7% (22/23)</td>
<td>78.6% (22/28)</td>
<td>17.1% (-2.9-35.5%)</td>
</tr>
<tr>
<td>CE</td>
<td>Clinical success @TOC</td>
<td>92.9% (13/14)</td>
<td>61.9% (13/21)</td>
<td>30.9% (1.1-52.7%)</td>
</tr>
<tr>
<td>CE</td>
<td>Micro success @TOC</td>
<td>100% (14/14)</td>
<td>80.0% (16/20)</td>
<td>20.0% (-4.6-41.6%)</td>
</tr>
</tbody>
</table>

• Probability of achieving target AUC/ MIC is 0% if vancomycin MIC = 2 µg/mL with low or high-dose vancomycin
• Vanco MICs of 2 µg/mL associated with ↑ vanco Rx failures¹
• “MIC creep” observed in some centers but not others²
  • Perhaps due to clonal dissemination or technical artifact

Survival to 90 Days
Cox Proportional Hazards

Predictors of mortality:
- Treatment with vancomycin*
- Malignancy
- Stroke/TIA
- ICU admission
- Decreased creatinine clearance

* $P = 0.001$

Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of MRSA Bacteremia

Vancomycin Combination Therapy

Cumulative AKI rate survival curve

VC: Vancomycin-Cefepime; VPT: Vancomycin-Piperacillin-tazobactam; AKI: Acute Kidney Injury

Pogue J. et al. *CID* 2016 (accepted for publication)
Frustrations with Vancomycin

Re: Vancomycin Therapy – agree that vancomycin is a terrible drug. After staffing ASP full-time for the last 6 months (a new service for us), my threshold to recommend alternatives is low, especially when vancomycin doses push beyond my comfort zone for nephrotoxicity (generally > 4 g/day), troughs are below goal even on aggressive dosing, and/or we have recurrent positive blood cultures. Unfortunately, we already have a lot of scrutiny on our daptomycin spend so we try to be judicious, but I agree – for myself or a family member, I would want alternative therapy.