Limitations of PK-PD in Clinical Trials: Focus on Vancomycin MIC and MRSA Infection

Vance G. Fowler, Jr., MD, MHS
<table>
<thead>
<tr>
<th>Nature of Relevant Financial Relationship</th>
<th>Commercial Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant or research support</td>
<td>Merck, Theravance, Cerexa, Pfizer, Novartis, MedImmune, Advanced Liquid Logics, National Institutes of Health</td>
</tr>
<tr>
<td>Paid consultant</td>
<td>Cerexa, Durata, Novartis, Merck, Pfizer, NovaDigm, The Medicines Company, MedImmune</td>
</tr>
<tr>
<td>Speaker’s Bureau</td>
<td>NONE</td>
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<tr>
<td>Employment</td>
<td>Duke University</td>
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<tr>
<td>Honoraria</td>
<td>Arpida, Astellas, Cubist, Inhibitex, Merck, Pfizer, Targanta, Theravance, Wyeth, Ortho-McNeil, Novartis, Vertex Pharmaceuticals</td>
</tr>
<tr>
<td>Membership on advisory committees or review panels, board membership, etc.</td>
<td>Merck Co-Chair V710 Vaccine</td>
</tr>
<tr>
<td>Ownership Interest (e.g., stocks, stock options or other interests)</td>
<td>NONE</td>
</tr>
<tr>
<td>Other relevant financial interests</td>
<td>NONE</td>
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</tbody>
</table>
Points of this Talk

- Association of Vanco MIC & Outcome in MRSA: Present, Complex, and Potentially Not Causal

- Clinical Benefit of AUC/MIC > 400: Unestablished
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MRSA Infection with Vanco MIC ≥1.5μg/mL Associated with Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High MIC≥1.5μg/mL</th>
<th>Low MIC&lt;1.5μg/mL</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bae et al (12)</td>
<td>13 events, 37 total</td>
<td>11 events, 28 total</td>
<td>0.84 [0.30, 2.31]</td>
</tr>
<tr>
<td>Choi et al (15)</td>
<td>4 events, 34 total</td>
<td>6 events, 36 total</td>
<td>0.67 [0.17, 2.60]</td>
</tr>
<tr>
<td>Haque et al (19)</td>
<td>41 events, 115 total</td>
<td>10 events, 43 total</td>
<td>1.83 [0.82, 4.08]</td>
</tr>
<tr>
<td>Hidayat et al (21)</td>
<td>12 events, 51 total</td>
<td>4 events, 44 total</td>
<td>3.08 [0.91, 10.37]</td>
</tr>
<tr>
<td>Holmes et al (23)</td>
<td>28 events, 94 total</td>
<td>16 events, 105 total</td>
<td>2.36 [1.18, 4.71]</td>
</tr>
<tr>
<td>Lalueza et al (32)</td>
<td>2 events, 13 total</td>
<td>14 events, 50 total</td>
<td>0.47 [0.09, 2.38]</td>
</tr>
<tr>
<td>Liao et al (34)</td>
<td>13 events, 40 total</td>
<td>46 events, 137 total</td>
<td>0.95 [0.45, 2.02]</td>
</tr>
<tr>
<td>Lodise et al (36)</td>
<td>12 events, 66 total</td>
<td>3 events, 26 total</td>
<td>1.70 [0.44, 6.61]</td>
</tr>
<tr>
<td>Musta et al (43)</td>
<td>60 events, 206 total</td>
<td>7 events, 36 total</td>
<td>1.70 [0.71, 4.10]</td>
</tr>
<tr>
<td>Neuner et al (45)</td>
<td>39 events, 186 total</td>
<td>1 event, 10 total</td>
<td>2.39 [0.29, 19.42]</td>
</tr>
<tr>
<td>Schweizer et al (50)</td>
<td>46 events, 341 total</td>
<td>3 events, 20 total</td>
<td>0.88 [0.25, 3.13]</td>
</tr>
<tr>
<td>Soriano et al (52)</td>
<td>37 events, 130 total</td>
<td>6 events, 38 total</td>
<td>2.12 [0.82, 5.49]</td>
</tr>
<tr>
<td>Takesue et al (53)</td>
<td>33 events, 97 total</td>
<td>62 events, 662 total</td>
<td>4.99 [3.04, 8.18]</td>
</tr>
<tr>
<td>van Hal et al (54)</td>
<td>38 events, 117 total</td>
<td>73 events, 236 total</td>
<td>1.07 [0.67, 1.73]</td>
</tr>
<tr>
<td>Wang et al (55)</td>
<td>13 events, 26 total</td>
<td>27 events, 97 total</td>
<td>2.59 [1.07, 6.30]</td>
</tr>
</tbody>
</table>

Total (95% CI): 1553 events, 1568 total, 100.0% mortality rate, Odds Ratio = 1.64 [1.14, 2.37].

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%

Test for overall effect: Z = 2.65 (P = .008)
Factors Associated with Treatment Outcomes

- **MSSA**
  - vancomycin [vs beta-lactams] \(^{1,4}\)
  - vancomycin MIC > 1.5 (independent of tx) \(^{11}\)
    - even when treated with beta-lactam (flucloxacillin)

- **MRSA**
  - prior vancomycin use \(^{16}\)
  - vancomycin cidal (vs static) \(^{16}\)
  - tPMP-1 \(^{16}\)
  - USA 300 strain \(^{15}\)
  - high vancomycin MICs \(^{5,10,15}\)
  - heteroresistance \(^{13}\)
  - infection site \(^{12}\)
  - Agr dysfunction \(^{14}\)
  - APACHE II ≥ 14 \(^{15}\)
  - AUC/MIC \(^{17,19}\)

1. Chang FY et al. Medicine (Baltimore) 2003;82:333
The Problem with MRSA Outcome Studies

THE BLIND MEN AND THE ELEPHANT
(A Hindoo Fable)

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The First approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The Second, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The Fourth reached out an eager hand,
And felt about the knee.
"What most this wondrous beast is like
Is mighty plain," quoth he;
"'Tis clear enough the Elephant
Is very like a tree!"
Complex Relationship Between MRSA & Mortality

Methicillin-resistant *Staphylococcus aureus*

**Bacterial Virulence and Fitness**

**Host Response**

**Time to Effective Antibiotic Therapy**

**Increased Mortality, Length of Stay and Costs**

**Differences in Antibiotic Efficacy**

**Comorbidities**

Vancomycin MIC-Mortality Association:

- Present in patients who never received vancomycin
  
  Holmes *J Infect Dis* 2011; 204: 340
  Cervera ICAAC 2012 Abst #K1122

- ↑ Vancomycin MIC = ↓ Virulence *In vivo*
  
  Cameron *J Infect Dis* 2012; 205: 1677

- ↑ Vancomycin MIC = ↓ Mortality in Clinic
  
  van Hal *PLoS One* 2011; 6:e21217
Vancomycin MIC Associated with 30 Day Mortality in MSSA Bacteremia

Vancomycin MIC Associated with 1 Year Mortality in MSSA Left-Sided Endocarditis

- MSSA treated with cloxacillin
  - Vancomycin MIC < 1.5: 18/53
  - Vancomycin MIC ≥ 1.5: 22/40
  - MRSA: 13/20

p = 0.027

Treated with vancomycin

% of mortality at one-year follow-up

Cervera ICAAC 2012 abst #1122
Take Home Pay: Vancomycin MIC & Outcome

- Present
- Complex
- Not Necessarily Causal
Points of this Talk

- Association of Vanco MIC & Outcome in MRSA: Present, Complex, and Potentially Not Causal

- Clinical Benefit of AUC/MIC > 400: Unestablished
The Recommendation

Based on these study results, an AUC/MIC ratio of \( \geq 400 \) has been advocated as a target to achieve clinical effectiveness with vancomycin.
## Summary of Studies comparing AUC/MIC to Clinical Outcome in Patients with *S. aureus* Infection

<table>
<thead>
<tr>
<th>Design</th>
<th>Infection type</th>
<th>MIC</th>
<th>Outcome</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Association between Outcome and AUC/MIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moise-Broder(^1)</td>
<td>Retrospective n=50 (Van Rx)</td>
<td>HAP/VAP MR/MSSA</td>
<td>BMD</td>
<td>Clinical &amp; Microbiological Success</td>
</tr>
<tr>
<td>Kullar(^2)</td>
<td>Retrospective n=320</td>
<td>MRSA Bacteremia</td>
<td>BMD</td>
<td>Composite: (30)-d death, (SAB&gt;7d), Symptoms</td>
</tr>
<tr>
<td>Brown(^3)</td>
<td>Retrospective n=50</td>
<td>MRSA IE/ Bacteremia</td>
<td>Etest</td>
<td>Attributable Mortality (n=8)</td>
</tr>
<tr>
<td><strong>No Association between Outcome and AUC/MIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuner(^4)</td>
<td>Retrospective n=222</td>
<td>MRSA Bacteremia</td>
<td>Etest</td>
<td>Persistent MRSAB (n=19)</td>
</tr>
<tr>
<td>Holmes(^5)</td>
<td>Prospective N=182</td>
<td><em>S. aureus</em> Bacteremia</td>
<td>BMD</td>
<td>30d Mortality (n=38)</td>
</tr>
</tbody>
</table>

\(^1\)Clin Pharmacokin 2004; 43:925; \(^2\)CID 2011; 52:975; \(^3\)AAC 2012; 56: 634; \(^4\)DMID 2010; 67:228; \(^5\)ICAAC11 #A1681
AUC/MIC $\geq 400$ Did Not Improve Outcome in MRSA Endocarditis Model

- 3 MRSA isolates with MIC 0.5, 1, and 2ug/mL each used to infect rabbits at control, regular dose, and high dose vanco (n=45 rabbits/isolate)

- After 2 days of VAN neither sterilization rate nor reduction in bacterial density in vegetations improved with Cmin levels of 15-20 mg/L or with AUC/MIC index $\geq 400$. 
Take Home Pay for AUC/MIC ≥ 400

- Clinical studies: no consensus

- Recent *in vivo* model: negative

- It is time to go beyond Monte Carlo Simulations and retrospective case control study design

- If the treatment effect is as big as the retrospective studies suggest, a large sample size in the definitive trial is unnecessary.
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