Efficacy and Safety of Linezolid vs. Daptomycin in Treatment of VRE Blood Stream Infections (BSI) and the Role of Combination Therapy with Beta-lactams

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Sinai Health System
Laboratory Medicine and Pathobiology, University of Toronto
Conflicts of Interest

• Co-developed workshop by AMMI Canada and Sunovion Pharmaceutical.
Objectives

• Contrast the efficacy and safety of linezolid vs. daptomycin in the treatment of vancomycin resistant Enterococci (VRE) blood stream infection (BSI).

• Review data for combination therapy with beta-lactams in the treatment of VRE BSI.

• Identify areas for future research.
Case #1

• 60 year old male with diabetes, coronary artery disease, peripheral vascular disease, in ICU post-op below-knee amputation.

• On day 5, develops fever, blood cultures are drawn, found to have VRE BSI.

• No evidence of endovascular infection.

• Unclear source – possibly central line vs. urine.

• VRE susceptible to daptomycin and linezolid with low MICs.
Audience Question

• Which antibiotic would you prescribe:

A. Linezolid.
B. Daptomycin 6 mg/kg/d.
C. Daptomycin 10-12 mg/kg/d.
D. Daptomycin + a β-lactam.
E. Not sure… that is why I am at this lecture at 7am on a Saturday!
What is Vancomycin Resistant Enterococcus (VRE)?

• Enterococci are a major colonizer of gut flora\(^1\) and can cause infection.

• Vancomycin resistance leaves few good therapeutic choices.\(^1,2\)

• Primarily spread in hospitals and rates in Canada are rising.\(^3\)

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Ontario VRE BSI Rates 2009-2018: All hospitals
CNISP: VRE BSI per 10,000 patient days Jan 2009 – June 2018

Courtesy of CNISP March 2019, unpublished, with permission
Who is at Risk for VRE BSI?

Patient- and hospital-level predictors of vancomycin-resistant Enterococcus (VRE) bacteremia in Ontario, Canada

Jennie Johnstone MD, PhD a,b,c,d,*, Cynthia Chen MSc a,c, Laura Rosella PhD a,d,e, Kwaku Adomako MSc a, Michelle E. Policarpio MSc a, Freda Lam MPH a, Chatura Prematunge MSc a, Gary Garber MD a,c,f on behalf of the Ontario VRE Investigators a
Patient-and hospital-level predictors of VRE bacteremia in Ontario-study results

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Charlson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Reference</td>
<td>.0002</td>
</tr>
<tr>
<td>1</td>
<td>2.37 1.5 – 3.73</td>
<td>.0002</td>
</tr>
<tr>
<td>≥2</td>
<td>6.65 4.59 – 9.64</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Length of Stay (Per Day)</td>
<td>1.11 1.09 – 1.13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ICU Admission</td>
<td>15.11 10.44 – 21.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All Cancer</td>
<td>5.97 3.08 – 8.97</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>119.57 16.16 – 884.92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-Bone Marrow Transplant</td>
<td>3.61 2.30 – 5.67</td>
<td>.045</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.17 1.59 – 6.33</td>
<td>.001</td>
</tr>
<tr>
<td>COPD</td>
<td>2.85 1.48 – 5.50</td>
<td>.002</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>6.46 3.74 – 11.16</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Solid Organ Transplant</td>
<td>30.53 12.85 – 72.53</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hospital Size (per 100 beds)</td>
<td>1.48 1.37 – 1.59</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Teaching Hospital</td>
<td>7.31 5.13 – 10.42</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Therapeutic Options for VRE

For BSI
- Linezolid
- Daptomycin
- Tigecycline
- Quinupristin/dalfopristin (only *E. faecium*)

In vitro activity
- Telavancin (only Van B VRE)
- Chloramphenicol
- Fosfomycin
- Nitrofurantoin
Linezolid

- **Class:** Oxazolidinone.
- **Effect:** Bacteriostatic.
- **MOA:** Binds to 50S subunit of bacterial ribosome to inhibit protein synthesis.
- **Resistance:** due to single base pair mutation in the 23S ribosomal RNA of 50S subunit, linezolid no longer able to bind.
- **Toxicities:** Headache, gastrointestinal disturbance, peripheral and optic neuropathy, serotonin syndrome, lactic acidosis, myelosuppression.

**Only agent FDA/Health Canada approved for treatment of VRE BSI**
Daptomycin

- **Class:** Cyclic lipopeptide class.

- **Effect:** Bactericidal activity, but optimal dose unknown (dose ranges from 6-12mg/kg/day); MICs in *Enterococcus* spp. higher than *S. aureus*.

- **MOA:** Binds to components of cell membrane causing efflux of intracellular cations.

- **Resistance:** Not fully elucidated.

- **Toxicities:** Myopathy, eosinophilic pneumonia, peripheral neuropathy.

## Concerns with Therapy

<table>
<thead>
<tr>
<th>Linezolid</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bacteriostatic</td>
<td>• Emergence of resistance during therapy</td>
</tr>
<tr>
<td>• Toxicity with prolonged</td>
<td>• Optimal dosing for VRE BSI unclear</td>
</tr>
<tr>
<td>exposure</td>
<td></td>
</tr>
</tbody>
</table>

Linezolid vs. Daptomycin for VRE BSI

- No systematic reviews of randomized controlled trials.
- No randomized controlled trials.
- 3 meta-analyses of observational studies with similar results.

Chuang YC et al. BMC Infect Dis 2014; 14: 687
RESEARCH ARTICLE

Daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bacteremia: systematic review and meta-analysis

Yu-Chung Chuang1, Jann-Tay Wang1*, Hsin-Yi Lin3 and Shan-Chwen Chang1

Chuang YC et al. BMC Infect Dis 2014; 14: 687
Potentially relevant studies identified and screened for retrieval (n = 803)

→ Review articles (n = 323)

Studies retrieved for title and abstract evaluation (n = 480)

→ Not original data reported (n = 111)
  Not relevant (n = 74)
  In vitro data (n = 85)
  Epidemiology study (n = 110)

Studies retrieved for full-text evaluation (n = 100)

→ Prophylaxis (n = 3)
  Pediatric study (n = 15)
  One arm in the same study (n = 68)
  Unacceptable (n = 1)

Studies included in the meta-analysis (n = 13)
Primary Outcome: Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>daptomycin</th>
<th>linezolid</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Furuya et al. 2005</td>
<td>5</td>
<td>14</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>El-Lababidi et al. 2007</td>
<td>12</td>
<td>28</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Dubrovskaya et al. 2008</td>
<td>13</td>
<td>40</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Marion et al. 2008</td>
<td>11</td>
<td>21</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Mave et al. 2009</td>
<td>8</td>
<td>30</td>
<td>14</td>
<td>68</td>
</tr>
<tr>
<td>Crank et al. 2010</td>
<td>31</td>
<td>67</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>Kraft et al. 2011</td>
<td>10</td>
<td>43</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>McKinnell et al. 2011</td>
<td>32</td>
<td>86</td>
<td>28</td>
<td>104</td>
</tr>
<tr>
<td>Bio et al. 2011</td>
<td>12</td>
<td>37</td>
<td>18</td>
<td>47</td>
</tr>
<tr>
<td>Lu et al. 2012</td>
<td>11</td>
<td>29</td>
<td>22</td>
<td>64</td>
</tr>
<tr>
<td>Twilla et al. 2012</td>
<td>15</td>
<td>63</td>
<td>25</td>
<td>138</td>
</tr>
<tr>
<td>Chou et al. 2012</td>
<td>9</td>
<td>16</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Barbour et al. 2013</td>
<td>23</td>
<td>58</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>532</td>
<td>656</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 192
Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.41, df = 12 (P = 0.67); I^2 = 0%
Test for overall effect: Z = 2.63 (P = 0.009)
Limitations of these 3 Meta-analyses

• All retrospective cohort studies.

• Small sample size.

• Range in daptomycin dosing (most were 6mg/kg/d).

• Confounding bias.
Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin-Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients

Nicholas S. Britt,1,2,3 Emily M. Potter,3 Nimish Patel,4 and Molly E. Steed1

Methods

• **Study design:** US national retrospective cohort study.

• **Population:** Veterans Affairs Medical Center patients in US 2004 – 2013.

• **Intervention:** linezolid vs. daptomycin for treatment of VRE-BSI.

• **Primary outcome:** treatment failure.
  • 30-day all-cause mortality; microbial failure; 60-day VRE-BSI recurrence.

• **Exclusions:** No linezolid/daptomycin; both linezolid/daptomycin; linezolid or daptomycin for <48 hrs.
### Table 2. Clinical Outcomes by Antimicrobial Treatment for Vancomycin-Resistant *Enterococcus* Bloodstream Infection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Linezolid (n = 319)</th>
<th>Daptomycin (n = 325)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>214 (67.1)</td>
<td>178 (54.8)</td>
<td>1.37 (1.13–1.67)</td>
<td>.001</td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>137 (42.9)</td>
<td>109 (33.5)</td>
<td>1.17 (1.04–1.32)</td>
<td>.014</td>
</tr>
<tr>
<td>Microbiologic failure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23 (14.6)</td>
<td>15 (6.4)</td>
<td>1.10 (1.02–1.18)</td>
<td>.011</td>
</tr>
<tr>
<td>60-day VRE-BSI recurrence</td>
<td>80 (25.1)</td>
<td>72 (22.2)</td>
<td>1.04 (.96–1.14)</td>
<td>.347</td>
</tr>
<tr>
<td>Early (7-day) mortality</td>
<td>41 (12.9)</td>
<td>23 (7.1)</td>
<td>1.07 (1.01–1.12)</td>
<td>.016</td>
</tr>
<tr>
<td>Hospital length of stay, d, median (IQR)</td>
<td>14 (7–25)</td>
<td>12 (6–25)</td>
<td>. . .</td>
<td>.228</td>
</tr>
<tr>
<td>Duration of bacteremia, d, median (IQR)</td>
<td>4 (2–7)</td>
<td>3 (2–5)</td>
<td>. . .</td>
<td>.033</td>
</tr>
</tbody>
</table>
Figure 1. Kaplan–Meier curves for outcomes (A) 30-day mortality and (B) microbiologic failure.
Table 5. Adverse Events by Antimicrobial Treatment Group for Vancomycin-Resistant *Enterococcus* Bloodstream Infection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Linezolid</th>
<th>Deptomycin</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia, No. (%)</td>
<td>18/285 (6.3)</td>
<td>14/284 (4.9)</td>
<td>1.30 (0.60–2.87)</td>
<td>.593</td>
</tr>
<tr>
<td>Creatine phosphokinase elevation, No. (%)</td>
<td>1/64 (1.6)</td>
<td>6/211 (2.8)</td>
<td>0.54 (0.01–4.81)</td>
<td>.974</td>
</tr>
</tbody>
</table>
Britt et al Commentary

• Overall step-forward.

• Median dose of daptomycin ~6mg/kg/day.

• Limitations:
  • Observational study.
  • Essentially all males.

Conclusion #1

Daptomycin (when doses of at least 6mg/kg/day used) not worse than Linezolid for treatment of VRE BSI, may be better.
Comparative Effectiveness and Safety of Standard-, Medium-, and High-Dose Daptomycin Strategies for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia Among Veterans Affairs Patients

Nicholas S. Britt,1,2 Emily M. Potter,3 Nimish Patel,4 and Molly E. Steed4,5

Objective

• **Primary aim:** To compare clinical and safety outcomes of various intensities of daptomycin dosing strategies on VRE BSI mortality.
Methods

• Retrospective cohort study of hospitalized adults with VRE BSI.

• Patients admitted between 2004 and 2014 to any Veterans Affairs medical centers.

• Exclusions: daptomycin treatment <48 hours, dose <5.5 mg/kg/day, hemodialysis; previous or concurrent treatment with another anti-VRE agent.

• Daptomycin dose definitions:
  • Standard dose: 6mg/kg/day; Medium dose: 8 mg/kg/day; High-dose: ≥10 mg/kg/day.
Safety

• CK elevation – no difference between groups (p=0.50):
  • Standard-dose daptomycin group, 6/441 (1.4%).
  • Medium-dose daptomycin group, 1/103 (1.0%).
  • High-dose daptomycin group, 0/51 (0.0%).
Conclusion #2

- Higher dose daptomycin appears more effective than lower dose daptomycin for VRE BSI.

- Higher doses of daptomycin does not have any apparent worsening of adverse events.
Effect of Daptomycin Dose on the Outcome of Vancomycin-Resistant, Daptomycin-Susceptible Enterococcus faecium Bacteremia

Yu-Chung Chuang, Hsin-Yi Lin, Pao-Yu Chen, Chi-Ying Lin, Jann-Tay Wang, Yee-Chun Chen, and Shan-Chwen Chang

Objectives

• **Primary aim:** To determine whether higher doses of daptomycin were more effective than customary doses in decreasing the mortality rate in VRE-BSI patients.

• **Secondary aim:** To determine whether a daptomycin MIC within the susceptible range could influence clinical outcomes.
Methods

• 2 hospitals in Taiwan.


• Decision about daptomycin dose was by prescribing physician.

• Exclusions:
  • <18 years, outpatients, daptomycin <72 hours.
**No difference between elevated CK levels in treatment groups (7/112 [6.3%] overall, p=0.99 between groups.**
Conclusion #3

Higher dose daptomycin appears more effective than lower dose daptomycin, irrespective of the VRE MIC.
Role of β-lactam synergy?

• β-lactams hypothesized to alter the surface charge of daptomycin non-susceptible strains of VRE to make the organism more likely to bind to daptomycin.

• May counteract some daptomycin non-susceptibility of VRE.

• Best β-lactam to choose is unclear.

Combination agent and concentration

8019 E. faecium

5938 E. faecium

Caution #1

• Clinical data supporting the addition of β-lactams for synergy are conflicting.
Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin-Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients

Nicholas S. Britt,1,2,3 Emily M. Potter,3 Nimish Patel,4 and Molly E. Steed1

Role of β-lactam + Daptomycin?

- Conducted an analysis of daptomycin-treated subjects with or without concomitant β-lactam treatment.

- Concomitant antibiotics included:
  - Ampicillin or ampicillin-sulbactam (n = 14).
  - Aztreonam (n = 13).
  - Cefazolin (n = 10), cefepime (n = 62).
  - Cefotaxime (n = 4), ceftazidime (n = 18), ceftriaxone (n = 35).
  - Imipenem-cilastatin (n = 49).
  - Doripenem (n = 8), ertapenem (n = 17), meropenem (n = 33).
  - Piperacillin-tazobactam (n = 96), ticarcillin-clavulanate (n = 10).

- No advantage observed in treatment:
  - β-lactam vs no β-lactam treatment failure: 56.3% [n = 135/240] vs 50.6% [n = 43/85]), p = .37.
A retrospective clinical comparison of daptomycin vs daptomycin and a beta-lactam antibiotic for treating vancomycin-resistant *Enterococcus faecium* bloodstream infections

Yu-Chung Chuang, Pao-Yu Chen, Chi-Ying Lin, Yee-Chun Chen, Jann-Tay Wang & Shan-Chwen Chang

Chuang YC et al. Scientific Reports 2018; 8: 1632.
Results

• 114 patients with VRE BSI received daptomycin:
  • 87 received daptomycin + β-lactam.
  • 27 daptomycin alone.

• Median daptomycin dose was 7.8 mg/kg/day.

• In daptomycin + β-lactam group, β-lactams included:
  • 10 (8.8%) received a penicillin.
  • 41 (36%) received a cephalosporin.
  • 62 (54%) received a carbapenem.
Failure of daptomycin β-Lactam combination therapy to prevent resistance emergence in *Enterococcus faecium*

Vidthiya Menon a, Rebecca Davis a, Nick Shackel b, Bjorn A. Espedido c, Alicia G. Beukers a,e, Slade O. Jensen c, Sebastiaan J. van Hal a

Case #1

• 60 year old male with diabetes, coronary artery disease, peripheral vascular disease, in ICU post-op below-knee amputation.

• On day 5, develops fever, blood cultures are drawn, found to have VRE BSI.

• No evidence of endovascular infection.

• Unclear source – possibly central line vs. urine.

• VRE susceptible to daptomycin and linezolid with low MICs.
Audience Question

• Which antibiotic would you prescribe:

A. Linezolid.
B. Daptomycin 6 mg/kg/d.
C. Daptomycin 10-12 mg/kg/d.
D. Daptomycin + a β-lactam.
E. Not sure… that is why I am at this lecture at 7am on a Saturday!
Case #2

• 60 year old male with diabetes, coronary artery disease, peripheral vascular disease, in ICU post-op below-knee amputation.

• On day 5, develops fever, blood cultures are drawn, found to have VRE BSI.

• No evidence of endovascular infection.

• Unclear source – possibly central line vs. urine.

• VRE susceptible to daptomycin but with an MIC 3 and linezolid susceptible.
Audience Question

• Which antibiotic would you prescribe:

A. Linezolid.
B. Daptomycin 6 mg/kg/d.
C. Daptomycin 10-12 mg/kg/d.
D. Daptomycin + a β-lactam.
E. Not sure… that is why I am at this lecture at 7am on a Saturday!
Case #3

• 60 year old male with diabetes, coronary artery disease, peripheral vascular disease, in ICU post-op below-knee amputation.

• On day 5, develops fever, blood cultures are drawn, found to have VRE BSI.

• No evidence of endovascular infection.

• Unclear source – possibly central line vs. urine.

• VRE non-susceptible to daptomycin (MIC 8) and linezolid susceptible.
Audience Question

• Which antibiotic would you prescribe:

A. Linezolid.
B. Daptomycin 6 mg/kg/d.
C. Daptomycin 10-12 mg/kg/d.
D. Daptomycin + a β-lactam.
E. Not sure… that is why I am at this lecture at 7am on a Saturday!
Future Studies

• Trial data needed:
  • Linezolid vs. daptomycin.
  • Optimal dose of daptomycin in VRE BSI + more robust evaluation of adverse events with high doses.
  • Role of β-lactams in combination with daptomycin.

• Generalizability of data
  • Canadians?
  • Pediatric populations?
Conclusions

• VRE BSIs are becoming more common in Canada.

• In susceptible isolates, daptomycin is likely a better choice than linezolid for treatment of VRE BSI.

• Optimal dosing of daptomycin unclear for VRE BSI, however, higher dosing appears better than lower dosing.

• Role of β-lactam synergy with daptomycin unclear, could consider adding when VRE MICs are not low.