Super Drug for a Super Bug,

The Debate Goes On and On:

Daptomycin Versus Linezolid for the Treatment of Vancomycin-Resistant Enterococcus Bacteremia

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Learning Objectives

1. Identify clinically relevant Enterococcus species and epidemiology
2. Describe the resistance mechanisms and risk factors for vancomycin-resistant Enterococcus infections
3. Discuss the current pharmacotherapy options for vancomycin-resistant Enterococcus bacteremia
4. Formulate an evidence-based recommendation regarding antibiotic choice for vancomycin-resistant Enterococcus bacteremia
I. Background

A. History\textsuperscript{1-3}

1899 – The term “enterocoque” first appeared in a paper from France and used to describe a diplococci organism found in gastrointestinal (GI) tract

1906 – Andrewes and Horde isolated “Streptococcus facaelis” from a patient with endocarditis

1933 – Enterococcus classified as Group D Streptococcus per Lancefield streptococci grouping based on carbohydrate antigens on cell wall

1984 – Schleifer and Kilpper-Balz identified Enterococcus as a separate genus using DNA homology thereby removing it from Lancefield Group D

Figure 1. Discovery of Enterococcus

B. Characteristics of enterococci\textsuperscript{1,4}

i. Gram-positive facultative anaerobe included in normal GI flora

ii. Also found on the skin, in the genitourinary (GU) tract, and in the oral cavity

iii. Oval shape which can be seen as single cells, pairs, and chains in various lengths

Figure 2. Enterococcus faecalis\textsuperscript{4}

1. Capable of growing in medium with the following characteristics
   a. High salt concentration 6.5% NaCl
   b. High pH 9.6
   c. Temperature between 10°C to 45°C
   d. Ability to hydrolyze esculin in the presence of 40% bile salts
      i. Differentiate between Streptococcus and Enterococcus
      ii. Hydrolyzed products, glucose and esculentin, will react with ferric citrate and produce insoluble iron salt, therefore, darkening the medium
2. Enterococci can survive for long periods on surfaces such as medical equipment and doorknobs
3. Tolerant to heat, chlorine, and alcohol
4. Resistant to a wide variety of antibiotics

C. Clinically relevant species\(^1,4\)

<table>
<thead>
<tr>
<th>Table 1. Clinically relevant species(^1,4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Enterococcus faecalis (E. faecalis)}</td>
</tr>
<tr>
<td>• Accounted for 90-95% of clinical isolates in the late 1970s with the introduction of third-generation cephalosporins</td>
</tr>
<tr>
<td>• Majority sensitive to ampicillin</td>
</tr>
<tr>
<td>• More virulent but easier to treat</td>
</tr>
</tbody>
</table>

II. Epidemiology

A. Prevalence\(^5\)

i. National Healthcare Safety Network (NHSN) 2009-2010 report on healthcare-associated infections (HAIs)

<table>
<thead>
<tr>
<th>Event</th>
<th>Number (%) of events reported 2007-2008 (n=47,582)</th>
<th>Number (%) of events reported 2009-2010 (n=69,475)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central line-associated bloodstream infections (CLABSIs)</td>
<td>18,651 (39.2)</td>
<td>27,766 (40)</td>
</tr>
<tr>
<td>Catheter-associated urinary tract infections (CAUTIs)</td>
<td>11,863 (24.9)</td>
<td>19,058 (27.4)</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia (VAP)</td>
<td>6,290 (13.2)</td>
<td>6,632 (9.5)</td>
</tr>
<tr>
<td>Surgical site infections (SSIs)</td>
<td>10,778 (22.7)</td>
<td>16,019 (23.1)</td>
</tr>
</tbody>
</table>

ii. Eight pathogen groups made up 80% of the infections
1. \textit{Staphylococcus aureus} 16%
2. \textit{Enterococcus} spp. 14%
   a. 35.5% of the enterococci were resistant to vancomycin
   b. Approximately 80% \textit{E. faecium} (1,709/2,069 isolates) and 10% \textit{E. faecalis} (245/2,578 isolates)
   c. Also second leading pathogen for CLABSI
3. \textit{Escherichia coli} 12%
4. Coagulase-negative staphylococci 11%
5. \textit{Candida} spp. 9%
6. \textit{Klebsiella} spp. 8%
7. \textit{Pseudomonas aeruginosa} 8%
8. \textit{Enterobacter} spp. 5%
B. VRE prevalence around the world

<table>
<thead>
<tr>
<th>Species</th>
<th>Percent of Enterococcus isolates resistant to vancomycin by region (no of isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Europe^2</td>
</tr>
<tr>
<td>E. faecium</td>
<td>8.8 (729)</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>1.0 (126)</td>
</tr>
<tr>
<td>All enterococci</td>
<td>4.0 (855)</td>
</tr>
</tbody>
</table>

III. Resistance Mechanisms

A. \(\beta\)-lactams^7-10

i. Intrinsic resistance

1. Low affinity of penicillin-binding proteins (PBPs), requires higher concentrations for adequate killing
   a. Responsible PBP for intrinsic resistance in \(E.\ faecalis\) is PBP4
   i. Most VRE \(faecalis\) remain susceptible to ampicillin
   b. Responsible PBP for intrinsic resistance in \(E.\ faecium\) is PBP5
      i. PBP5 is a multi-functional PBP
      ii. Ability to overproduce PBP5 and continue with cell wall synthesis, which facilitates resistance to ampicillin

2. Tolerance
   a. Removal of reactive oxygen species by superoxide dismutase
   b. Lack of killing despite growth inhibition
c. β-lactams should not be used as monotherapy for infection with endovascular complications, such as endocarditis

ii. Acquired resistance
   1. Plasmid-mediated *bla* genes encode for β-lactamases
      a. Identical to those of *Staphylococcus aureus* (*S. aureus*)
      b. Predominately in *E. faecalis*
      c. Can be overcome by adding β-lactamase inhibitor
   2. PBP4/5 point mutations further decrease binding affinity, especially problematic in *E. faecium*

B. Aminoglycosides\textsuperscript{7-10}
   i. Intrinsic low-level resistance
      1. Low uptake limits inhibition of ribosomal protein synthesis
      2. More common with *E. faecalis*
      3. Uptake of this drug class, specifically gentamicin or streptomycin, can be enhanced by cell wall agent (synergy for endocarditis treatment)
   ii. Acquired high-level resistance
      1. Modified ribosomal attachment site
      2. Acquisition of genes that encode for enzymes that modify and inactivate aminoglycosides
      3. More common with *E. faecium*
      4. Resistance to gentamycin and streptomycin precludes use of these agents for synergism

C. Streptogramin: quinupristin-dalfopristin (Synercid\textsuperscript{®})\textsuperscript{7-10}
   i. First drug approved by Food and Drug Administration (FDA) for VRE *faecium* in 1999
   ii. Indication was removed in 2010 due to lack of data
   iii. Intrinsic resistance: *E. faecalis* utilizes drug efflux
   iv. Acquired resistance: *E. faecium*
      1. Drug modification via acetylation of streptogramin A
      2. Target modification via demethylation of the 23S rRNA
      3. Efflux pumps

D. Glycopeptide: vancomycin (Vancocin\textsuperscript{®})\textsuperscript{7-10}
   i. First identified VRE isolate was found in United States (U.S.) in 1986, roughly 15 years after vancomycin introduction
   ii. Acquired resistance: modification of the peptidoglycan precursors from D-ala to D-lactate, which results in 1,000 fold decrease in binding affinity
   iii. VanA cassette (widely distributed and predominate type of resistance)
      1. Resistance induced by both vancomycin and teicoplanin
      2. Mostly carried by *E. faecium*
      3. Implicated in vancomycin-resistant *S. aureus*
1. Van S: activated by the presence of glycopeptides through auto-phosphorylation leading to phosphorylation of Van R
2. Van R: phosphorylated Van R promotes Van H, A, X, Y, Z transcription (also augments the transcription of itself and Van S)
3. Van H: converts pyruvate to D-lactate
4. Van A: ligates D-ala to D-lactate
5. Van X: breakdown D-ala-D-ala to its amino acid constituents
6. Van Y: removal of remaining D-ala terminus on the peptidoglycan precursor
7. Van Z: unknown, but might be responsible for resistance to teicoplanin

IV. Risk Factors for VRE

A. Use of broad-spectrum antibiotics and/or multiple courses of antibiotics leads to\textsuperscript{1,7}
   i. Downregulation of intestinal RegIIIγ expression
      1. RegIIIγ is a C-type lectin produced by highly specialized intestinal epithelial cells, Paneth cells, in the presence of gram-negative organisms
      2. RegIIIγ has antimicrobial activity against Gram-positive bacteria, including VRE
ii. Increased colonization density in GI tract by *Enterococcus* species, including VRE, following antibiotic treatment\textsuperscript{11}
   a. Two weeks after antibiotics cessation, an increase in the populations of *Clostridium*, *Enterococcus*, and Enterobacteriaceae were noted
   b. VRE remains as the predominate species for up to two months
B. Extended hospitalization, including nursing home facilities
C. Close proximity to patients with VRE
D. Immunocompromised patients, including solid organ and bone marrow transplants
E. High Acute Physiology and Chronic Health Evaluation (APACHE) II scores
F. Comorbidities that require hemodialysis or an urinary catheter

V. VRE Bacteremia and Treatment Options

![Diagram](image)

*Figure 6.* Colonization in the GI tract precedes bloodstream infections\textsuperscript{7}

A. Bacteremia is a common presentation of enterococcal infection
B. Sources of bacteremia\textsuperscript{4}
   i. Catheter-related bloodstream infections (CRBSIs)
   ii. Non-CRBSIs
      1. GI infection
      2. GU infection
      3. Wound
      4. Hepatobiliary tracts
      5. Intraabdominal and pelvic foci
C. Vancomycin resistance is associated with failure to clear bacteremia and a 2-3 fold increase in mortality when compared to vancomycin-sensitive enterococcal bacteremia\textsuperscript{12}
D. Effective antibiotic therapy shortens the period of infection thereby decreasing mortality, which can be greater than 60% among critically ill and neutropenic patients.13

E. Currently, there are no formal guidelines for the treatment of VRE bacteremia
   i. Prevention, prevention, prevention14
      1. Active surveillance to identify the carrier
      2. Appropriate contact precaution for infected and colonized patients
      3. Antimicrobial stewardship
      4. Strict hand and environment hygiene
      5. Education program for healthcare workers
   ii. Source control is the first priority15,16
      1. Drainage of infected fluid
      2. Debridement of infected tissues
      3. Remove infected devices such as indwelling catheters
      4. Surgical intervention such as valve replacement for endocarditis
   iii. Anti-VRE agents19,20
      1. Choice of agent is based on resistance profile
         a. Ampicillin-sensitive
         b. Ampicillin-resistant, ampicillin-sulbactam sensitive
         c. Ampicillin-resistant, vancomycin-sensitive
         d. Ampicillin-sensitive, vancomycin-resistant
e. **Ampicillin-resistant and vancomycin-resistant**
   2. Commonly prescribed agents for ampicillin-resistant VRE
      a. Linezolid
      b. Daptomycin
      c. No randomized-controlled trials available to provide a definitive answer to which agent is the optimal antibiotic for VRE-BSI
         i. Two Phase-III clinical trials were aborted due to lack of enrollment
         ii. No plan for clinical trials in the future at this time
<table>
<thead>
<tr>
<th>Year Approved</th>
<th>Linezolid (Zyvox®)</th>
<th>Daptomycin (Cubicin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2000</td>
<td>2003</td>
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<table>
<thead>
<tr>
<th>Class</th>
<th>Oxazolidinone</th>
<th>Cyclic lipopeptide</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Oral and intravenous</th>
<th>Intravenous</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>MOA</th>
<th>Inhibits bacterial protein synthesis by binding to the initiation complex</th>
<th>Binds to components of the cell membrane, causes rapid depolarization and cell death</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cidality</th>
<th>Bacteriostatic against <em>Staphylococcus</em> and <em>Enterococcus</em>, bactericidal against <em>Streptococcus</em></th>
<th>Bactericidal, concentration-dependent</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Gram-positive, including VRE</th>
<th>Gram-positive, including VRE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>FDA approved indications</th>
<th>VRE bacteremia</th>
<th>Right-sided endocarditis due to <em>S. aureus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumonia</td>
<td><em>S. aureus</em> bloodstream infection</td>
</tr>
<tr>
<td></td>
<td>SSSIs, both uncomplicated and complicated</td>
<td>SSSIs, complicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Adult: 600 mg every 12 hours</th>
<th>Adult: 4-6 mg/kg once a day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pediatric: 10 mg/kg every 8 hours</td>
<td>Pediatric: not first-line, avoid in &lt;1 year old</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic</th>
<th>Absorption: rapid and extensive, 100% bioavailability</th>
<th>Distribution: 0.1 L/kg; critically-ill patients 0.23 ± 0.14 L/kg; protein binding: ~90%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distribution: 40-50 L; protein binding: ~30%</td>
<td>Excretion: renal</td>
</tr>
<tr>
<td></td>
<td>Metabolism: hepatic via oxidation</td>
<td>t_{1/2}: 8-9 hours, up to 28 hours in renal impaired</td>
</tr>
<tr>
<td></td>
<td>Excretion: nonrenal</td>
<td>Linear kinetic</td>
</tr>
<tr>
<td></td>
<td>t_{1/2}: 3-5 hours</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal</th>
<th>No dose adjustment needed</th>
<th>CrCl &lt;30 mL/min: 4-6 mg/kg every 48 hours</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>Hepatic</th>
<th>No dose adjustment needed</th>
<th>No dose adjustment needed</th>
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<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Myelosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transient, reversible, dose and time-dependent</td>
</tr>
<tr>
<td></td>
<td>Higher incidence when treatment lasts ≥14 days</td>
</tr>
<tr>
<td></td>
<td>Discontinue with worsening myelosuppression</td>
</tr>
<tr>
<td></td>
<td>Monitor myelosuppression</td>
</tr>
<tr>
<td></td>
<td>Monitor CBC at least weekly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Serotonin syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPK elevation and myopathy</td>
</tr>
<tr>
<td></td>
<td>Seen with original twice daily dosing</td>
</tr>
<tr>
<td></td>
<td>Discontinue with symptoms of myopathy and CPK 5X ULN or 10X ULN without symptoms</td>
</tr>
<tr>
<td></td>
<td>Monitor CPK at least weekly</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Eosinophilic pneumonitis (rare)</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Resistance</th>
<th>MIC breakpoint: ≤2 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate: as low as 3% and as high as 20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Mutation in the central loop of domain V of the 23S rRNA</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Methylation of rRNA with Cfr gene</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Resistance</th>
<th>MIC breakpoint: ≤4 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate: as low as 2% and as high as 15%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Altered membrane-bound protein through cardiolipin synthetase, GdpD, and liaFSR genes</th>
</tr>
</thead>
</table>

MOA = mechanism of action; SSSIs = skin and skin structure infections; t_{1/2} = half-life; CrCl = creatinine clearance; IAI = intraabdominal infections; CBC = complete blood count; CPK = creatine phosphokinase; ULN = upper limit normal; MIC = minimum inhibitory concentration
Table 5. Studies that evaluate the safety and/or efficacy of daptomycin at higher doses\textsuperscript{33-36}

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design/ Treatment Regimen</th>
<th>Study Population</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Figueroa, et al. 2009 | Single center, retrospective chart review; \( n=61; \) daptomycin >6 mg/kg/day; mean dose=8 mg/kg; median duration=25 days | Patients received daptomycin >6 mg/kg/day for ≥14 days; various infections                             | • 22/61 experienced adverse events but did not require discontinuation  
  • 3/61 had CPK level >1000 U/L plus symptoms after 24-28 days of treatment and had to discontinue daptomycin  
  • Significant CPK level was found in 3/34 (8.8%) patients who had close CPK analysis | Most patients were symptomatic when significant CPK level elevation occur                              |
| Moise, et al. 2009 | Multicenter, retrospective, observational; \( n=94; \) daptomycin dose ≥8 mg/kg/day              | CORE database; patients with various gram-positive infections                                           | • Response rate for bacteremia was 91%  
  • Clinical cure rate for VRE was 89%  
  • Adverse event rate attributable to daptomycin was 6.4%, with 3.2% for elevated CPK level | Daptomycin dose of ≥8 mg/kg may be safe and effective                                                |
| Kullar, et al. 2011 | Multicenter, retrospective, observational, case series analysis; \( n=250; \) daptomycin dose ≥8 mg/kg/day | Patients with confirmed or suspected S. aureus and/or enterococcal infections at any site, who had received high-dose daptomycin for at least 72 hours  
  • 87.2% bacteremia  
  • 24.3% were VRE faecium | • 84% clinical cure rate  
  • 80% microbiologic cure rate  
  • Adverse event rate attributable to daptomycin was 1.2% | Daptomycin dose of ≥8 mg/kg was safe and well-tolerated with no dose-response relationship to changes in CPK |
| Hall, et al. 2012 | In vitro PK/PD study                                                                             | Tested 3 different strains of enterococci against daptomycin and linezolid in simulated endocardial vegetation | • Linezolid demonstrated bacteriostatic activity  
  • Both daptomycin 6 and 8 mg/kg failed to maintain bactericidal activity  
  • Rapid bactericidal activity from daptomycin 10 and 12 mg/kg was sustained | Daptomycin dose ≥10 mg/kg/day may be necessary to treat VRE endocarditis                             |

CORE=Cubicin Outcomes Registry and Experience; CPK= creatine phosphokinase; PK=pharmacokinetic; PD=pharmacodynamics

F. Clinical Question: In the absence of randomized-controlled trials, what is the optimal therapy for VRE bacteremia in the setting of ampicillin resistance?
**VI. Literature Review**

### Table 6. Systematic reviews and meta-analyses

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Study Design</th>
<th>Study characteristics/Drawbacks</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Whang, et al. 2013| Retrospective; 9 studies and n=1,074 | - 8 studies in U.S. and 1 study in Taiwan  
- 2/9 were abstracts  
- Did not adjust for confounders | No statistical significant difference found between linezolid and daptomycin for clinical cure, microbiologic cure, and mortality |
| Balli, et al. 2014| Retrospective; 10 studies and n=967 | - 8/10 studies were included in Whang, et al.  
- 4/10 were abstracts  
- Mis-classified Furuya et al. | Daptomycin is associated with higher mortality in VRE bacteremia  
No statistically significant difference found between linezolid and daptomycin for adverse events |
| Chuang, et al. 2014| Retrospective; 13 studies and n=1,188 | - 10/13 studies were included in Balli, et al.  
- 11 studies in U.S. and 2 studies in Taiwan  
- 4/13 were abstracts | Daptomycin was associated with significantly higher mortality when the pooled adjusted OR was used  
No statistically significant difference found between linezolid and daptomycin for clinical and microbiologic cure rates  
Daptomycin was found to have statistically significant higher relapse rate  
No statistically significant difference found between linezolid and daptomycin for adverse events  
Found high heterogeneity between the conference abstracts |

All 3 systematic reviews included studies that differ in: cohorts, definition of VRE-BSI, definition of mortality, outcomes reported, daptomycin dosing

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**Objective**

Summarize available evidence and provide estimates of the clinical effectiveness of linezolid versus daptomycin for the treatment of VRE bacteremia through meta-analysis.

**Design**

Systematic review and meta-analysis to quantify differences in clinical outcomes from VRE-BSI treated with daptomycin or linezolid
- Searched MEDLINE, EMBASE, CENTRAL, ISI Web of Science, and SCOPUS until August 2012
- Reviewed abstracts from annual meetings of IDSA, ICAAC, ECCMID, ICID from 2003-August 2012
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009

**Population**

**Inclusion criteria**
- Studies comparing the outcomes of treatment between daptomycin and linezolid for VRE bacteremia in two groups of patients
- Studies providing data on patient mortality outcomes
- Patients ≥18 years old

**Outcomes**

**Primary outcome:** 30-day all-cause mortality, infection-related mortality, in-hospital mortality, and composite overall mortality
**Secondary outcome:** clinical cure, microbiological cure, recurrence of VRE bacteremia, and adverse events

**Statistics**
- Odds ratio (OR) with 95% confidence interval (CI) for each study was calculated
- Mantel-Haenszel model used for fixed-effect method and Dersimonian and Laird for random-effects method
• X² statistic to assess variation between study-to-study
• Funnel plot analysis and Egger’s test for publication bias
• Sensitivity analyses for mortality adjusted for important confounders through multivariate logistic analyses
• Additional sensitivity analysis performed to remove studies that included patients switched from one agent to the other

Results

n= 10 retrospective studies → 967 VRE-BSI patients → 429 in daptomycin and 538 in linezolid

Baseline characteristics
• Varying definitions of VRE-BSI and mortality
• Primary outcome was stated in only five of the studies
• Sample size range from 31-201 patients
• Linezolid dose: 600 mg every 12 hours, median duration of therapy=11-15 days
• Median Daptomycin dose: 6 mg/kg (3.4-10.4 mg/kg), median duration of therapy=13-15 days

| Table 7. Results of meta-analysis of studies comparing daptomycin to linezolid for VRE-BSI |
|-----------------|-----------------|-----------------|
|                  | # of Studies    | # of Patients   | OR (95% CI)   |
| **Primary Outcomes** |               |                |               |
| 30-day All-cause Mortality | 4             | 232/311        | 1.61 (1.08-2.4) |
| Infection-related Mortality | 2             | 68/68          | 3.61 (1.42-9.2) |
| In-hospital Mortality | 3             | 116/142        | 1.83 (1.05-3.2) |
| Overall Mortality | 10            | 408/538        | 1.41 (1.06-1.89) |
| **Secondary Outcomes** |                |                |               |
| Clinical Cure | 3             | 128/213        | 1.04 (0.63-1.72) |
| Microbiological Cure | 6             | 219/331        | 0.75 (0.41-1.39) |
| Recurrence of VRE Bacteremia | 4             | 139/232        | 2.51 (0.94-6.72) |
| Adverse Events LFT > 2 x ULN | 1             | 43/29          | 0.31 (0.1-0.98) |

D=daptomycin; L=linezolid

Author’s conclusion
Daptomycin may be associated with worse outcomes than linezolid in patients treated for VRE bacteremia.

Critique

**Strengths**
• Searched several databases
• Clear inclusion criteria
• Large sample size
• Multivariable regression analyses were performed in 6/10 studies to adjust for potential confounders

**Limitations**
• Screened for titles only which may overlook relevant articles
• Included conference abstracts with missing information and were not peer reviewed
• Studies selected for systematic reviews differ in cohort, outcomes examined, inclusion and exclusion criteria, daptomycin dose used, and definition of VRE-BSI and mortality
• Heterogeneity among pooled studies makes it difficult to adjust for confounding factors
• Many studies included patients who were under-dosed on daptomycin and three studies did not report daptomycin dose
• Contacted the authors of eight studies to obtain information, but only received three responses
• All the included studies noted a trend toward daptomycin treatment among patients with neutropenia, thrombocytopenia and endocarditis (treatment selection bias)
• Misclassified Furuya et al. and did not include it in the adjusted OR group for overall mortality outcome

Take home point
Based on this study, daptomycin is associated with higher mortality in VRE bacteremia. However, several limitations make the validity of the conclusion questionable.

*IDSA= Infectious Disease Society of America; ICAAC= Interscience Conference on Antimicrobial Agents and Chemotherapy; ECCMID= European Congress of Clinical Microbiology and Infectious Diseases; ICID= International Congress on Infectious Diseases*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Period</th>
<th>Study Size (L/D)</th>
<th>Patient Population</th>
<th>Linezolid (mg; twice daily)</th>
<th>Daptomycin Mean Daily Dose (range; mg/kg)</th>
<th>Statistically Significant Confounder</th>
<th>Outcomes (clinical cure, microbiologic cure, and mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio, et al.*</td>
<td>2004-2008</td>
<td>84 (47/37)</td>
<td>VRE-BSI and received linezolid or daptomycin ≥3 days</td>
<td>600</td>
<td>6 (3.7-8.8)</td>
<td>Thrombocytopenic patients in daptomycin; ICU patients in linezolid</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>Crank, et al.*</td>
<td>2003-2007</td>
<td>101 (34/67)</td>
<td>VRE-BSI</td>
<td>600</td>
<td>5.5</td>
<td>Daptomycin group had patients with shock, previously on vancomycin or linezolid</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>Dubrovskaya, et al.**</td>
<td>2005-2007</td>
<td>80 (40/40)</td>
<td>VRE-BSI and received linezolid or daptomycin ≥2 days</td>
<td>NA</td>
<td>6 (4-9)</td>
<td>Hematologic malignant and neutropenic patients in daptomycin</td>
<td>Statistically significant higher mortality found with daptomycin</td>
</tr>
<tr>
<td>Furuya, et al.**</td>
<td>2004-2005</td>
<td>54 (40/14)</td>
<td>VRE-BSI</td>
<td>NA</td>
<td>5.7 (3.9-7.9)</td>
<td>Not reported</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>Kraft, et al.</td>
<td>2004-2006</td>
<td>72 (29/43)</td>
<td>VRE-BSI and received linezolid or daptomycin ≥2 days, hematology or BMT</td>
<td>NA</td>
<td>NA</td>
<td>Bone marrow transplant in daptomycin; acute myeloid leukemia in linezolid</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>Mave, et al.*</td>
<td>2003-2007</td>
<td>98 (68/30)</td>
<td>VRE-BSI</td>
<td>600</td>
<td>6</td>
<td>ICU patients in daptomycin</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>McKinnell, et al.*</td>
<td>2005-2008</td>
<td>235 (104/86)</td>
<td>VRE-BSI and received linezolid or daptomycin ≥2 days</td>
<td>NA</td>
<td>NA</td>
<td>Neutropenic patients in daptomycin</td>
<td>Statistically significant higher mortality found with daptomycin</td>
</tr>
<tr>
<td>Twilla, et al.</td>
<td>2004-2009</td>
<td>201 (138/63)</td>
<td>VRE-BSI and received linezolid or daptomycin ≥3 days</td>
<td>600</td>
<td>6.1 (3.4-10.4)</td>
<td>Hematologic malignant and liver transplant in daptomycin; older patients in linezolid</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>El-Lababidi, et al.%</td>
<td>2000-2006</td>
<td>56 (28/28)</td>
<td>VRE-BSI</td>
<td>NA</td>
<td>NA</td>
<td>Patients received chemotherapy in daptomycin</td>
<td>No statistically significant difference found</td>
</tr>
<tr>
<td>Marion, et al.**</td>
<td>2005-2007</td>
<td>31 (10/21)</td>
<td>VRE-BSI, febrile neutropenia</td>
<td>600</td>
<td>6</td>
<td>Not reported</td>
<td>No statistically significant difference found</td>
</tr>
</tbody>
</table>

* = multivariable logistic regression analysis was performed to adjust for potential confounders; *=abstract; ICU=intensive care unit; NA=not applicable
Objective: Compare the safety and effectiveness of linezolid versus daptomycin for treatment of VRE-BSI

Design: National retrospective cohort study of hospitalized patients admitted to any Veterans Affairs Medical Center (VAMC) between January 2004 and January 2013

Population
- **Inclusion criteria**
  - Patients ≥18 years old with at least one blood culture positive for VRE
- **Exclusion criteria**
  - Treatment with another anti-VRE agent
  - Treatment with linezolid and daptomycin combination therapy (including sequential)
  - Treatment with daptomycin or linezolid for <48 hours

Outcomes
- **Primary**: treatment failure, composite of
  - 30-day all-cause mortality
  - Microbiologic failure
  - Recurrence of VRE-BSI within 60 days of therapy completion
- **Secondary**:
  - Early seven-day mortality
  - Hospital length of stay (LOS)
  - Duration of bacteremia

Adverse events: platelet and creatine phosphokinase (CPK) data were collected from the start of treatment until three days after the end of therapy

Methods
- Data were extracted from inpatient, outpatient, and administrative databases from all VAMCs
- $\chi^2$ or 2-tailed Fisher exact test were used to compare baseline categorical variables
- t test or Mann-Whitney U test were used to compare continuous variables
- Poisson regression model used to determine if antimicrobial treatment was independently associated with clinical outcomes
- Kaplan-Meier method with log-rank test and Cox proportional hazards models were used for time-to-event analyses of 30-day all-cause mortality and microbiologic failure
- Mantel-Haenszel procedure used to stratified for VRE-BSI species (E. faecalis or E. faecium) and source of infections

Results: $n=644$, all were resistant to ampicillin → 325 in daptomycin group and 319 in linezolid group

**Baseline characteristics**
- Statistically significant differences between the two groups: age ≥65, ICU, mechanical ventilation, higher APACHE II score, and duration of therapy
- Linezolid dose: 600 mg twice a day, median duration of therapy=7 days
- Median daptomycin dose: 5.93 mg/kg, median duration of therapy=11 days

<table>
<thead>
<tr>
<th>Table 9. Clinical outcomes by antimicrobial treatment for VRE-BSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
</tr>
<tr>
<td>Treatment Failure</td>
</tr>
<tr>
<td>30-day All-cause Mortality</td>
</tr>
<tr>
<td>Microbiologic Failure*</td>
</tr>
<tr>
<td>60-day VRE-BSI Recurrence</td>
</tr>
</tbody>
</table>

**Secondary Outcomes**
- Early (7-day) Mortality                                     | 41 (12.9)         | 23 (7.1)           | 1.07 (1.01-1.12)   | 0.016   |
- Hospital LOS, median (IQR)                                  | 14 (7-25)         | 12 (6-25)          | NA                 | 0.228   |
- Duration of Bacteremia, median (IQR)                        | 4 (2-7)           | 3 (2-5)            | NA                 | 0.033   |

*≥1 follow-up blood culture during treatment period: linezolid n=157, daptomycin n=233; NA=not applicable

- Propensity score matching supported study findings that linezolid had a significantly higher incidence of treatment failure compared to daptomycin (RR 1.25, 95% CI 1.04-1.5), higher microbiologic failure rate (RR 1.81, 95% CI 1.09-3.03) and longer duration of bacteremia (P=0.038)
- No statistically significant difference found between linezolid and daptomycin on thrombocytopenia and CPK elevation

**Author’s conclusion**
Treatment with daptomycin for VRE-BSI was associated with significantly less treatment failure, microbiologic failure, and a shorter duration of bacteremia.

**Critique**

**Strengths**
- Multicenter national cohort investigation of VRE-BSI treatment
- Electronic data extraction from all VAMCs
- Homogeneous patient population
- Poisson regression, Cox proportional analysis, and propensity score matching were conducted to adjust for treatment selection and confounders

**Limitations**
- Majority of the patients were older male adults limiting generalizability
- Several statistically significant differences found between baseline characteristics
- Standard but not optimal daptomycin dose was used
- Statistically significant difference between duration of therapy with linezolid’s median duration well-under labelled recommendation
- Only 60% of the cohort had follow-up cultures and most were in the daptomycin group
- Adverse effects may be underestimated because patients with sequential therapy were excluded and only objective laboratory data were collected

**Take home point**
In a subset of the study population, daptomycin was associated with shorter duration of bacteremia and better outcomes.

**VII. Summary of Literature**

A. There are many small retrospective studies comparing linezolid and daptomycin for VRE-BSI and the majority found no differences due to small sample sizes
B. Lack of homogeneity coupled with inconsistent findings in the three systematic reviews and meta-analyses, which were conducted to overcome small sample sizes in individual studies, resulted in no definitive conclusion
C. Britt et al. successfully adds data to challenge findings from the recent systematic reviews and meta-analyses

**VIII. Conclusions**

A. Clinical challenges
   i. VRE-BSI remains a serious complication of hospitalization with treatment challenges
   ii. 6 mg/kg is the common dose used in clinical practice, however, higher doses of daptomycin (≥8 mg/kg and up to 12 mg/kg) have shown to improve clinical outcomes without causing a significant increase in adverse events
B. Both agents remain acceptable options for VRE-BSI
C. Studies that compare linezolid and higher doses of daptomycin are warranted
D. Patient status and adverse effects from long-term use are also important considerations
E. In the absence of “gold-standard” prospective, randomized-controlled trials, a well-conducted retrospective study like Britt et al. can provide some guidance on VRE-BSI treatment choices
F. Propose algorithm

**Figure 7.** Non-endovascular bacteremia treatment algorithm
IX. References


