Combination treatment for MDR gram-positive infections

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GISA website at: www.antimicrobialstewardship.net
Disclosures 2017

- **Advisory Board**: Angelini, MSD, Nordic Pharma
- **Speaker/chairman**: Angelini, Astellas, Basilea, MSD, Pfizer
- **Events Sponsorship**: Astellas, Gilead, MSD, BMS, Jansenn, ViiV, BioMerieux, Biotest, Becton-Dickinson, Nordic Pharma, Pfizer, Shionogi
- **Ongoing research protocol**: Angelini, Astellas, Cidara, MSD, Shionogi, Theravance
Trend of blood isolates, Toscana 2015-2016

- *S. pneumoniae*
  - 2016: 1166
  - 2015: 656
- *S. aureus*
- *P. aeruginosa*
- *K. pneumoniae*
- *E. coli*
  - 2016: 656
  - 2015: 335
- *E. faecium*
- *E. faecalis*
- *Acinetobacter spp.*
- *Candida spp.*
Toscana 2016

*S. aureus*: 1166 blood isolates, MRSA: 32%
C) *Staphylococcus aureus* meticillino-resistente (MRSA) Toscana, anno 2016. Fonte: ARS-SMART, ECDC
MRSA: terminology

- **MRSA**: resistant to all beta-lactams except ceftaroline & ceftobiprole
- **CA-MRSA**: community-acquired, tend to be antibiotic susceptible, except to macrolides & FQs
- **HA-MRSA**: hospital-acquired; tend to be multiple drug resistant
- **VISA**: vancomycin MIC 4-8 mg/l
- **hVISA**: hetero-resistant sub-population
- **VRSA**: MIC > 8 mg/l
- **PVL**: Panton-Valentine leucocidin
- **Livestock-associated MRSA**: may infect humans
MRSA infections

- Bacteremia
- Endocarditis (native, prosthetic valve)
- Pneumonia
- Osteomyelitis
- Prosthetic joint infection
- Septic arthritis
- ABSSSI
Drawbacks of the current therapeutic options for MRSA

**Vancomycin**
- Available for parenteral use only
- MIC creep
- Difficulties in attainment of therapeutic levels
- Emergence of VISA, hVISA, VRSA

**Daptomycin**
- Available for parenteral use only
- Not indicated for treatment of pneumonia

**Linezolid**
- Bacteriostatic
- Significant drug interactions
- Myelosuppressive
Rationale of Combination Antibiotics

- Broad-spectrum empiric treatment for life-threatening infections
- Treatment of polymicrobial infections
- Minimization of drug toxicity by using relatively low doses of the two drugs
- Synergistic inhibitory & bactericidal activities *
- Prevention of emergence of antibiotic resistance (?)

* Antibiotic synergy refers to a net increase of antimicrobial effect resulting from the interaction of 2 drugs that is greater than the sum of their independent contributions
Synergistic activities

• A beta-lactam increase intracellular uptake of AGs leading to enhanced killing and bactericidal activity in GPC.
• Drugs acting at various levels of peptidoglycan synthesis (eg, β-lactams, fosfomycin, glycopeptides, and lipopeptides).
• Synergistic PAEs: β-lactams with Ags; RFP plus other classes of drugs.
• Prolongation of PAE: higher protection against organism regrowth in situations when one or both antibiotics become subtherapeutic during the dosing interval.
Disadvantages of combination therapy

- Potential antagonism
- Risk of emergence of other resistant organisms
- *Clostridium difficile* infection
- Increased cost of therapy
- Increased risk of adverse effects*

*Short-course, low-dose GM combined with VANCO for MRSA bacteremia and native valve endocarditis and in combination with other β-lactams may be associated with an increased risk of nephrotoxicity.*
MRSA bacteremia: treatment failure

Consider use of combination therapy *

- Prolonged or relapsing bacteremia
- Endocarditis
- Undrained focus
- Vancomycin MIC > 2 mg/l

* daptomycin (HD) plus beta-lactams (oxacillin, ceftaroline, etc.); fosfomycin plus imipenem

* The Sanford Guide 2018
Salvage therapy options for MRSA
Daptomycin and β-Lactam CombinationTherapy

• The “seesaw” effect (improved β-lactam activity when DAP susceptibility decreases)

• Synergy: β-lactam ↑ the net surface negative charge on the bacterial cell wall leading to ↑ binding of the daptomycin-Ca2+ complex, resulting in synergy and ↑ killing of MDR gram-pos.

• β-lactam ↑ killing by various cationic host defense peptides (HDPs): β-lactams sensitize MRSA for ↑ clearance by HDP and phagocytes and ↑ the synergistic activity between β-lactams and daptomycin.

• Prevention of emergence of resistance: β-lactams along with dapto prevent the emergence of resistance to dapto in clinical MRSA isolates and in enterococci.
Unique role for advanced generation cephalosporins (ceftaroline, ceftobiprole)

- Unlike other β-lactams, ceftaroline & ceftobiprole has activity against MRSA, hVISA, VISA, VRSA, and DNS S aureus mediated by binding to PBP2a, with 128 times greater affinity than any other clinically available β-lactam.
- Because PBP2a on the cell surface decreases with reduced glycopeptide and lipopeptide susceptibility, the enhanced activity of daptomycin mediated by ceftaroline or ceftobiprole is likely a result of synergistic activity as well.
Sakoulas et al. reported on the salvage therapy with daptomycin plus ceftaroline in 26 patients with persistent S. aureus bacteraemia (median 10 days; range 3–23 days).

The most common source of bacteraemia was IE (n.14; left-sided, 12 patients) with 22 infections due to MRSA. (2 VISA, 4 DNS.

Upon initiation of daptomycin plus ceftaroline, bacteraemia cleared in a median of 2 days (range 1–6 days).

Barber et al. confirmed this synergistic activity in an in vitro biofilm model, revealing that this combination displayed therapeutic enhancement against MRSA biofilms.
# Ceftaroline for Severe Methicillin-Resistant *Staphylococcus aureus* Infections: A Systematic Review

Reese A. Cosimi, Nahal Beik, David W. Kubiak, and Jennifer A. Johnson

1Department of Pharmacy, Massachusetts General Hospital, 2Center for Drug Policy, Partners Healthcare, 3Department of Pharmacy, and 4Division of Infectious Diseases, Brigham and Women’s Hospital, Boston, Massachusetts; and 5Harvard Medical School, Cambridge, Massachusetts

<table>
<thead>
<tr>
<th>Authors</th>
<th>Combination Therapy</th>
<th>Treatment</th>
<th>Patient Population</th>
<th>Patient No.</th>
<th>Study Design</th>
<th>Clinical Success Rate</th>
<th>Median Time to Culture Clearance</th>
<th>Ceftaroline related-ADE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose, Schulz, Andes. 2012. [23]</td>
<td>CPT 200mg q12h + DAP 6mg/kg q48h</td>
<td><em>S. aureus</em> IE</td>
<td>1</td>
<td>Case report</td>
<td>100%</td>
<td>4 days</td>
<td>None reported</td>
<td>Patient died after culture clearance due to comorbidities</td>
<td></td>
</tr>
<tr>
<td>Baxi, Chan, Jain. 2015. [24]</td>
<td>CPT 400mg q12h + DAPb</td>
<td><em>S. aureus</em> IE</td>
<td>1</td>
<td>Case report</td>
<td>100%</td>
<td>11 days</td>
<td>None reported</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sakoulas et al. 2014. [25]</td>
<td>CPT 200mg q12h-600mg q8h + DAPb</td>
<td>Staphylococcal bacteremia</td>
<td>26</td>
<td>Case series</td>
<td>96%</td>
<td>2 days</td>
<td>None reported</td>
<td>1 patient died due to comorbidities</td>
<td></td>
</tr>
<tr>
<td>Cunha, Gran. 2015. [26]</td>
<td>CPT 600mg q12h + DAP 12mg/kg q24h</td>
<td>MRSA prosthetic-valve IE</td>
<td>1</td>
<td>Case report</td>
<td>100%</td>
<td>4 days</td>
<td>None reported</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sundragiri, Vallabhajosyula, Haddad. 2015. [27]</td>
<td>CPT + DAPc</td>
<td>MRSA IE</td>
<td>1</td>
<td>Case report</td>
<td>0%</td>
<td>No clearance</td>
<td>None reported</td>
<td>Patient remained septic and died eventually</td>
<td></td>
</tr>
</tbody>
</table>
Salvage therapy options for MRSA  
Vancomycin + β-lactam combination therapy

• Time–kill studies demonstrated that vanco combined with ceftaroline was more potent than dapto plus ceftaroline:
• Results from a multicentre trial from Australia (CAMERA trial*) supported the use of combo for MRSAB, with 60 patients randomly assigned to receive vancomycin alone (n.29) or vancomycin plus flucloxacillin (n.31).
• The mean duration of bacteraemia was shorter in the combination versus standard therapy group (1.94 versus 3 days), with fewer patients having persistence at days 3 and 7 in the combination arm.
Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Pilot Multicenter Randomized Controlled Trial

the Combination Antibiotics for MEthicillin Resistant *Staphylococcus aureus* (CAMERA) study group; and for the Australasian Society for Infectious Diseases Clinical Research Network

HR, 0.74 (95% CI, 0.49–1.26); log-rank *P* = .14

<table>
<thead>
<tr>
<th>Time, d</th>
<th>Standard</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients at Risk, No.

Salvage therapy options for MRSAB
Linezolid + β-lactam

- Park et al*. done a prospective observational study evaluating salvage therapy in pts with persistent MRSAB.
- Patients were continued on a vanco based regimen or linezolid was substituted for vanco, with or without a CP.
- Of 377 MRSAB episodes, 90 were persistent, and 38 were switched to linezolid monotherapy (n.19) or together with a carbapenem (n.19) after persistence of bacteraemia for a median of 16 days (range 10–24 days).
- Early microbiological response was achieved in 17/38 (45%) and treatment success in 28/38 (74%) pts.
- Linezolid-based pts had a significantly lower 30 day mortality compared with vanco-based pts (11% versus 25%; P<0.008).

*Journal of Infection, Volume 65, Issue 6, December 2012, Pages 505-512
Salvage therapy options for MRSAB: Fosfomycin + imipenem

- A multicentre trial was conducted in Spain* consisting of 16 patients who were treated with 2 g of fosfomycin IV every 6 h plus 1 g of imipenem IV every 6 h as salvage treatment in MRSAB.
- All patients cleared their blood within 72 h, with a clinical success rate of 69%, and the regimen was well tolerated.
- Fosfomycin may be considered as a component of a combination salvage therapy for MRSAB in countries where the parenteral formulation is available.

Trimethoprim/sulfamethoxazole + ceftaroline

• A greater bacteraemic persistence was observed with T/S monotherapy compared with vancomycin.
• A case series evaluated patients with MRSAB that failed initial therapy and were switched to T/S plus ceftarolne.
• The source of infection was endovascular (65%), consisting of 15 cases with IE (4 right-sided, 11 left-sided).
• Microbiological success was achieved in 90%, with a success rate of only 31% (due in part to 25% patients lost to follow-up).
• While showing some promise, trimethoprim/sulfamethoxazole use does warrant an element of caution due to potential haematological adverse effects, associated hyperkalaemia and the uncertainty surrounding dosing in renal insufficiency.
## New anti gram-positives antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>cSSSi</th>
<th>CAP</th>
<th>HAP</th>
<th>VAP</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftarolina Zinforo</td>
<td>Pfizer</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>No VAP 600 mg bid</td>
</tr>
<tr>
<td>Ceftobiprole Mabelio</td>
<td>Cardiome Pharma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>No VAP 500 mg tid</td>
</tr>
<tr>
<td>Telavancina * Vibativ</td>
<td>Astellas</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Once-daily 10 mg/Kg No IR * When alternative treatment is not suitable</td>
</tr>
<tr>
<td>Dalbavancin Xydalba</td>
<td>Angelini</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>IV single dose 1500mg</td>
</tr>
<tr>
<td>Oritavancin Orbactiv</td>
<td>The Medicines Company</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>IV Single dose 1200 mg</td>
</tr>
<tr>
<td>Tedizolid Sivextro</td>
<td>MSD</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>200 mg IV/OS X 6 days</td>
</tr>
</tbody>
</table>
The data support the potential use of oritavancin in combination with BLs, especially oritavancin in combination with ceftaroline, for the treatment of infections caused by MRSA.
**In vitro** activity of daptomycin combined with dalbavancin and linezolid, and dalbavancin with linezolid against MRSA strains

**Table 1.** MIC values of antimicrobial agents for 30 MRSA strains and susceptibility rates

<table>
<thead>
<tr>
<th></th>
<th>MIC values (mg/L)</th>
<th></th>
<th></th>
<th></th>
<th>Susceptibility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;range&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>1</td>
<td>1</td>
<td>0.5 – 1</td>
<td></td>
<td>100&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>0.12</td>
<td>0.12</td>
<td>0.03 – 0.12</td>
<td></td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1</td>
<td>2</td>
<td>1 – 2</td>
<td></td>
<td>100&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table 2.** Interpreted FICI results and distributions of FICI values of the antimicrobial combinations against 30 MRSA strains

<table>
<thead>
<tr>
<th>Combination</th>
<th>Interpreted FICI results, n (%)</th>
<th>Distributions of FICI values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>synergism</td>
<td>no interaction</td>
</tr>
<tr>
<td>Dalbavancin/linezolid</td>
<td>18 (60)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Dalbavancin/daptomycin</td>
<td>20 (67)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Daptomycin/linezolid</td>
<td>20 (67)</td>
<td>10 (33)</td>
</tr>
</tbody>
</table>

*J Antimicrob Chemother* 2017; 72: 441–443
The future for MRSA

Newer oxazolidinones:
Cadazolid: *Clostridium difficile* infection
*Radezolid*: high intracellular concentration, active against linezolid-resistant isolates of *S. aureus*

New tetracyclines:
*Eravacycline*
*Omadacycline*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Advantages</th>
<th>Drawbacks</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer fluoroquinolones</td>
<td><em>ABSSSI, CAP, sexually transmitted infections</em></td>
<td>Broad spectrum, activity in acidic pH</td>
<td>Some agents exhibit higher MIC for quinolone resistant isolates</td>
<td>Currently undergoing evaluation in clinical trials</td>
</tr>
<tr>
<td>Lefamulin</td>
<td><em>ABSSSI, CAP</em></td>
<td>Broad Gram-positive spectrum and fastidious Gram-negative bacteria</td>
<td>Does not cover <em>E. faecalis</em>, susceptible to <em>cfr</em> gene mediated resistance</td>
<td>Currently undergoing evaluation in clinical trials</td>
</tr>
</tbody>
</table>
E. faecalis: 656 blood isolates

ARS-SMART
E. faecium: 335 blood isolates
VRE: 18,5%

ARS-SMART
VRE Bloodstream infections (BSI)

- VRE-BSI can be a lethal complication for hospitalized patients.
- VRE-BSI principally affects vulnerable populations, including complex postsurgical and internal medicine pts with multiple comorbid conditions.
- VRE-BSI has particularly high attributable mortality in hematopoietic stem cell transplant recipients, liver transplant recipients, oncology patients, and other critically-ill hospitalized populations.

Juwon Yim, Jordan R. Smith, Michael J. Rybak, 2017
VRE in HSCT

• VRE is increasingly recognized as a major pathogen in HSCT recipients.
• The reported cumulative incidence of post-transplant VRE bacteremia in allo-HSCT recipients at U.S. centers is 6%-16%.
• VRE bacteremia in this population typically occurs in the setting of broad-spectrum antimicrobial exposures during the neutropenic period, which leads to an absence of normal enteric bacteria and intestinal domination with VRE.
• Although VRE is typically considered to be a relatively avirulent pathogen, it sometimes causes bacteremia and septic shock in neutropenic HSCT recipients.

Satlin & Walsh, 2017
# Antibiotic regimen for endocarditis

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Preferred regimen</th>
<th>Altern. regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amp S</td>
<td>Amp + AG</td>
<td>Van + AG</td>
</tr>
<tr>
<td></td>
<td>Amp + CRO</td>
<td></td>
</tr>
<tr>
<td>Amp R/Van S</td>
<td>Van + AG</td>
<td>LZD (+AG)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapto + Amp</td>
</tr>
<tr>
<td>Amp R/Van R</td>
<td>Dapto HR + Amp</td>
<td>LZD (+AG)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapto + Ceftaroline</td>
</tr>
<tr>
<td>Amp R/Van R/AG R</td>
<td>Dapto HR + Amp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dapto HR + Ceftaroline</td>
<td></td>
</tr>
</tbody>
</table>
Sinergism ampicillin + ceftriaxone
Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating Enterococcus faecalis Infective Endocarditis

Nuria Fernández-Hidalgo,1 Benito Almirante,1 Joan Gavaldà,1 Mercè Gurgui,2 Carmen Peña,3 Arístides de Alarcón,4 Josefa Ruiz,5 Isidre Vilacosta,6 Miguel Montejo,7 Nuria Vallejo,8 Francisco López-Medrano,9 Antonio Plata,10 Javier López,11 Carmen Hidalgo-Tenorio,12 Juan Gálvez,13 Carmen Sáez,14 José Manuel Lomas,15 Marco Falcone,18 Javier de la Torre,16 Xavier Martínez-Lacasa,17 and Albert Pahissa1

Table 3. Outcomes of 246 Episodes of Enterococcus faecalis Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ampicillin + Ceftriaxone (n = 159)</th>
<th>Ampicillin + Gentamicin (n = 87)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death during treatment</td>
<td>35 (22%)</td>
<td>18 (21%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Death during 3-mo follow-up</td>
<td>13 (8%)</td>
<td>6 (7%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Adverse effects requiring treatment withdrawal</td>
<td>2 (1%)</td>
<td>22 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment failure requiring change of antimicrobials</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Relapse</td>
<td>3/124 (3%)</td>
<td>3/69a (4%)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* These patients had received 28, 36, and 42 days of ampicillin plus gentamicin, respectively.
VRE-BSI: linezolid

• Linezolid is the only drug specifically approved by the FDA for the treatment of VRE-BSI. However, studies leading to approval were based on limited data.
• Linezolid is a bacteriostatic agent, and its activity may not be ideal for patients with severe VRE infections including infective endocarditis and other endovascular infections.
• Linezolid may not be optimal in deep-seated VRE infections
• Linezolid toxicity when administered for prolonged courses may limit its use in VRE endocarditis.

Juwon Yim, Jordan R. Smith, Michael J. Rybak, 2017
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>
VRE-BSI: Daptomycin pitfalls

- Emergence of resistance during therapy, particularly in HSCT pts. One major cancer center reported that 15% of their VRE bloodstream isolates were daptomycin-non-susceptible.
- Daptomycin is not an effective therapy for pneumonia because it is inactivated by alveolar surfactants.
- Weekly monitoring of CPK is recommended, as almost 3% of pts receiving daptomycin developed elevated levels.
- Optimal DAP dosing for VRE infections has not been established with some in vitro data suggesting that doses of 10–12 mg/kg should be used to prevent development of resistance
Figure 2. Mortality at different daptomycin doses and minimum inhibitory concentrations. Abbreviations: MIC, minimum inhibitory concentration; Q1, first dose quartile; Q2, second dose quartile; Q3, third dose quartile; Q4, fourth dose quartile.
VRE: Daptomycin plus β-lactams

- Recent investigations suggest that DAP non susceptible enterococci may be more prone to be killed by the combination of DAP and β-lactams, despite the fact that they exhibit high MICs to ampicillin.
- This synergistic effect has been observed with ampicillin, ceftaroline, and most recently with ertapenem.
- Although the mechanistic basis for such synergism are obscure, the addition of β-lactam may improve the avidity of DAP for its cell membrane target by altering the surface charge.
β-Lactam combinations with daptomycin provide synergy against vancomycin-resistant Enterococcus faecalis and Enterococcus faecium

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Combination regimen for VRE

- Dapto in combo with ceftaroline or ertapenem seems to hold the most promise on in vitro studies and case reports.
- The addition of β-lactams not only potentiates the bactericidal activity of dapto but also prevents development of dapto nonsusceptibility in enterococci.
- For the emergence of dapto nonsusceptibility in enterococci associated with dapto monotherapy, high-dose dapto, up to 10-mg/kg/day, combined with a β-lactam antibiotic appears to be a reasonable therapeutic choice.
- Daptomycin combination therapy with β-lactams should be considered in cases of deep-seated VRE infections.
Case in point from real-life

- Female, 80 years-old,
- vascular encephalophaty, chronic AF
- Mitral bioprotesis, 2007
- Agust 2015: UTI (?) treated with Augmentin,
- *E. faecalis* relapsing bacteremias  (*october 2015, January & April 2016*) Teicoplanina, Ampicillin + GM
- Ecocardiography TTE/TEE & Tc/PET negatives !!!!!!
- May 2016 admitted in ID: da *E. faecalis* bacteremia; Ampi S, HLR-GM
- Tc/PET: SUV 6,5 on mitralic bioprosthesis
- NO pheripheral embolism
Case in point from real-life

- Treated with AMPI + CRO x 6 weeks
- Blood cultures negatives, discharged to home
- September 2016 (2 months after ATBT stop) Tc/PET: SUV reduction (6.5 → 4.3)
- Admitted for re-evaluation: blood cultures again positive for *E faecalis*, same sensitivity profile
- Treated with AMPI + DAPTO (sinergism with E-test) x 10 days
- Need for an early discharge; MIC dalbavancina (E-test): 0.047
- Dalbavancin 1500 mg EV every 2 weeks
- Chronic suppressive therapy with Augmentin 1gx 3 → 1gx 2
- 1 year follow-up: no fever, persistently negative blood cultures.
Some (tentative) conclusions

• For MRSA persisting bacteremia: combination for salvage therapy
• Several suggestions from “in vitro” data but clinical evidence limited
• Daptomicin (or vancomycin) plus a betalactam (ceftaroline) seems to be the preferred regimen
• For enterococci: combination antibiotic therapy is the rule, especially for endocarditis but also for VRE bacteremia in the compromised host
• (HD) Daptomycin plus a betalactam seems to be preferable regimen in difficult to treat infections