Deaf or Dead? Is It Time To Drop Aminoglycosides For Dual β-Lactam Therapy In Enterococcal Infective Endocarditis?

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Learning Objectives:
1. Define the specific characteristics of enterococcal infective endocarditis
2. Explain the current evidence regarding β-lactam/aminoglycoside combination therapy and the surrounding controversy
3. Evaluate the current literature regarding dual β-lactam synergy and its effectiveness in enterococcal endocarditis
I. Infective Endocarditis (IE)
   a. Background\textsuperscript{1,2}
      i. First described in 1885 by Sir William Osler
      ii. Bacterial infection of the endocardium/inner heart lining
      iii. 1/3 of patients die within the first year of diagnosis
   b. Epidemiology/Etiology\textsuperscript{2,3}
      i. 30-100 episodes per 1 million patient years
      ii. Male predominance
      iii. Median age of diagnosis: 58 years
      iv. Different populations affected in industrialized/developing countries
   c. Common predisposing factors\textsuperscript{2,3}
      i. Native valve abnormality (32%)
      ii. Recent invasive procedure (27%)
      iii. Congenital heart disease (12%)
      iv. Intravenous drug use (10%)
   d. Pathophysiology\textsuperscript{2-4}
      i. Predisposing structural abnormalities of cardiac valve
      ii. Adhesion of circulating bacteria to valvular surface
      iii. Adherent bacteria survive and propagate
   e. Microbiology\textsuperscript{2,5}
      i. \textit{Staphylococcus} (~44%) and \textit{streptococcus} (~38%) species account for most IE cases
      ii. Enterococci third leading cause of IE
         1. Most common in patients with concomitant gastrointestinal & genitourinary infections
         2. Accounts for 5-11% of endocarditis cases\textsuperscript{6}
      iii. Gram negative IE (~10%) – difficult to treat and requires diligence with cultures
      iv. Fungal IE uncommon with poor prognosis
      v. Culture negative IE (~10%)
   f. Diagnosis\textsuperscript{2}
      i. Accurate diagnosis or rejection of IE is based on presence of major/minor criteria
         and pathological data according to the modified Duke strategy
         1. Definitive IE (Major Criteria)
            a. Blood culture positive for IE
            b. Evidence of endocardial involvement
         2. Possible IE
            a. Mixture of major criteria and minor criteria (fever, predisposing heart condition, vascular phenomena etc.)

II. Enterococcal Infective Endocarditis (EIE)
   a. Presentation\textsuperscript{6-8}
      i. Sub-acute course (fever, malaise, murmur)
      ii. Predisposing heart condition (86%)
      iii. Co-morbid conditions (45.4%)
      iv. Aortic valve locus with heart failure (34%)
      v. Genitourinary tract source of initial infection (32%)
      vi. Hospital acquisition (27%)
   b. Mortality rates remain unchanged over the last 30 years (~20%)\textsuperscript{6,7}
c. *Enterococcus* spp.
   i. Gram positive cocci long regarded as harmless commensal organisms of gastrointestinal tract\(^9,10\)
   ii. Originally a member of *Streptococcus* genus belonging to Lancefield’s group D\(^11\)
      1. *Streptococcus faecalis* first coined in 1906\(^12\)
      2. Morphologically and phenotypically similar to *Streptococcus*\(^13\)
      3. Revised in 1984 to separate *Enterococcus* genus\(^11\)
   iii. Diverse group of bacteria\(^14\) with at least 18 species\(^13\)
   iv. Exceedingly hardy organisms that tolerate a wide variety of growth conditions\(^15\)
   v. Resistant to many antibiotics
      1. Most antibiotics show consistent inhibitory, but not bactericidal, activity
      2. Effective therapy often requires synergy of dual antimicrobials
   vi. *E. faecalis* most common Enterococcal pathogen in infective endocarditis\(^6,14\)
   vii. *E. faecium* IE rare despite commonly causing bacteremia: lack of adhesion/aggregation properties
   viii. Also *E. gallinarum*, *E. durans* *E. avium* and *E. hirae*
   d. Susceptibility to vancomycin, aminoglycosides and ampicillin varies between isolates\(^9,14,16\)
   e. Effective therapy often requires synergy of antimicrobial combinations

III. Aminoglycosides
   a. Amikacin, tobramycin, gentamicin, streptomycin etc.
   b. Disrupt bacterial protein synthesis through ribosomal binding\(^17\)
      i. Concentration dependent killing
      ii. Most effective against rapidly multiplying bacteria
   c. Multiple resistance mechanisms\(^17-19\)
      i. Reduced uptake/cell permeability
      ii. Altered ribosomal binding sites
      iii. Enzymatic modification
   d. High Level Aminoglycoside Resistance (HLAR)\(^17,18\)
      i. Normal aminoglycoside minimum inhibitory concentration (MIC): 4-256 μg/ml
      ii. HLAR MIC >500 μg/ml (gentamicin) or >2,000 μg/ml (streptomycin)
      iii. Most often mediated by aminoglycoside modification
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Literature Review of Historical β-lactam/aminoglycoside Combinations</th>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geraci, et al.</td>
<td>1954</td>
<td>• 33 cases of EIE from 1944-1953&lt;br&gt;• Monotherapy with penicillin or streptomycin = failure&lt;br&gt;• 6 weeks of penicillin + streptomycin found to be synergistic and bactericidal</td>
<td></td>
</tr>
<tr>
<td>Mederski et al.</td>
<td>1983</td>
<td>• First reports of enterococci strain with HLAR&lt;br&gt;• Described resistance pattern of 200 Enterococcal isolates&lt;br&gt;• 57% resistant to one or more aminoglycosides&lt;br&gt;• Aminoglycoside resistance precludes synergistic effect of β-lactam combination</td>
<td></td>
</tr>
<tr>
<td>Wilson, et al.</td>
<td>1984</td>
<td>• 12 year prospective study (1970-1981): 56 patients with EIE&lt;br&gt;• Patients received 28 days of β-lactam/aminoglycoside therapy with doses adjusted for renal function and serum concentrations&lt;br&gt;• Overall relapse rate 12.5%; relapse higher in streptomycin resistant isolates (penicillin/gentamicin combination)&lt;br&gt;• Gentamicin nephrotoxicity: 60%&lt;br&gt;• Increased mortality with streptomycin-resistant isolates (penicillin/gentamicin combination) and patients presenting with symptoms &gt;3 months</td>
<td></td>
</tr>
<tr>
<td>Olaisson, et al.</td>
<td>2002</td>
<td>• 5 year prospective study (1995-1999) of 93 cases of definite IE&lt;br&gt;• 81% clinical cure&lt;br&gt;• Median treatment duration:&lt;br&gt;• 42 days of cell-wall active agent (β-lactam, vancomycin)&lt;br&gt;• 15 days of aminoglycoside combination therapy&lt;br&gt;• 7 patients received no aminoglycoside therapy and experienced no relapse&lt;br&gt;• 16% mortality, 3% relapse&lt;br&gt;• Mortality not associated with shortened aminoglycoside course&lt;br&gt;• Conclusions: shortened aminoglycoside course to avoid nephrotoxic effects can been used without negative clinical consequences</td>
<td></td>
</tr>
<tr>
<td>Dahl, et al.</td>
<td>2013</td>
<td>• 84 consecutive patients with definite left sided <em>E. faecalis</em> IE (2002-2011)&lt;br&gt;• Treatment intervention: 2 weeks v 4-6 weeks of gentamicin combination&lt;br&gt;• All patients treated with β-lactam/gentamicin combination&lt;br&gt;• Majority of patients received aminoglycosides once daily&lt;br&gt;• No difference in 1 year event-free survival&lt;br&gt;• Lower hospital mortality in shortened therapy group (10% v 5%; p=NS)&lt;br&gt;• Extended therapy group had significantly lower renal function at discharge&lt;br&gt;• Conclusions: Treatment of <em>E. faecalis</em> with 2 weeks of combination β-lactam/gentamicin therapy has similar outcomes as 4-6 weeks of therapy</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1:** Comparison of survival rates between patients treated before and after 2007.
V. Timeline of Enterococcal IE and β-lactam/aminoglycoside combination

1942: penicillin G

1943: streptomycin

1940-50's: IE monotherapy met largely with failure

1954: penicillin/streptomycin combination has synergy

1970's: gentamicin

1984: Up to 81% of EIE isolates streptomycin resistant

1980's: gentamicin replaces Streptomycin in βL/AG combo

1995: AHA guidelines recommend 4-6 weeks AG combination

2000's: Short course AG therapy equally efficacious

2005: AHA guidelines recommend 4-6 weeks AG combination
VI. 2005 AHA Guidelines on Infective Endocarditis
   a. Grading of recommendations
      i. Classification of recommendations
         1. Class 1 – Conditions for which there is evidence or general agreement that a given treatment is useful and effective
         2. Class 2 – Conditions for which there is conflicting evidence or a divergence of opinion that a given treatment is useful and effective
            a. Class 2A – Weight of evidence is in favor of usefulness
            b. Class 2B – Usefulness is less well established by evidence
      ii. Level of evidence
         1. A – Derived from multiple randomized trials
         2. B – Data derived from a single randomized trial or non-randomized studies
         3. C – Consensus opinion of experts
   b. Therapy determined by antimicrobial susceptibility/resistance pattern

Figure 2

Susceptible to PCN/GENT/VANC
- Ampicillin/Aq Pen G + Gentamicin (4-6wk)[1A]
- Vancomycin + Gentamicin (6wk)[1B]*only if PCN allergic

PCN Resistant
- β-Lactamase isolate
  - Ampicillin/subactam + Gentamicin (6wk)[2A-C]
  - Vancomycin + Gentamicin (6wk)[2A-C]*only if PCN allergic
- PCN Resistant
  - Vancomycin + Gentamicin (6wk)[2A-C]

Resistant to PCN/GENT/VANC
- E. faecium
  - Linezolid(>8wk)[2A-C]
  - Quinupristin/dalfopristin(>8wk)[2A-C]
- E. faecalis
  - Imipenem/cilastatin + Ampicillin(>8wk)[2B-C]
  - Ampicillin + Ceftriaxone (>8wk)[2B-C]

GENT Resistant
- Ampicillin/Aq Pen G + Streptomycin (4-6wk)[1A]
- Vancomycin + Streptomycin (6wk) [1B]*only if PCN allergic

Enterococcal IE
VII. Evidence Behind Dual β-lactam Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Details</th>
</tr>
</thead>
</table>
| Mainardi et al. | 1995 | • 50 clinical isolates of *E. faecalis*  
• Bacteriostatic and synergistic effect found between amoxicillin and cefotaxime regardless of amoxicillin or aminoglycoside susceptibility  
• Mechanism for synergy proposed  
• No synergistic effect for *E. faecium* |

| Gavalda et al.  | 1999 | • 10 clinical isolates of *E. faecalis* with HLAR in rabbit endocarditis model  
• Evaluated efficacy of ampicillin/ceftriaxone combination  
• Human-like pharmacokinetic model similar to 2gm IV ampicillin/ceftriaxone  
• Reduction of ampicillin MICs was observed when combined with sub-inhibitory concentrations of ceftriaxone  
• Combination resulted in significantly lower bacterial titers in cardiac vegetations with sterilization of vegetation in 47% |

Susceptibilities *E. faecalis* strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>A (MIC μg/mL)</th>
<th>C (MIC μg/mL)</th>
<th>A/C</th>
<th>Synergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>E51</td>
<td>2</td>
<td>&gt;1024</td>
<td>0.25</td>
<td>+</td>
</tr>
<tr>
<td>E61</td>
<td>2</td>
<td>&gt;1024</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>V45</td>
<td>1</td>
<td>512</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>E365</td>
<td>4</td>
<td>1024</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>E74</td>
<td>2</td>
<td>1024</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>E81</td>
<td>4</td>
<td>&gt;1024</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>E10</td>
<td>4</td>
<td>&gt;1024</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>E78</td>
<td>2</td>
<td>1024</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>E17</td>
<td>2</td>
<td>1024</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>V48</td>
<td>1</td>
<td>256</td>
<td>0.06</td>
<td>+</td>
</tr>
</tbody>
</table>

A: Ampicillin; C: Ceftriaxone; A/C: Ampicillin + Ceftriaxone

VIII. Dual β-lactam synergy\(^{25,27}\)

- Low amoxicillin concentrations
  1. Partial saturation of essential penicillin binding proteins (PBPs) 4 and 5
  2. Non-essential PBPs 2 and 3 are unbound and allowed to rebuild cell wall
- Cefotaxime saturates PBPs 2 and 3 at lower concentrations and PBPs 1, 4 and 5 at higher concentrations
- Synergistic combination yields partial saturation of PBPs 4 and 5 by amoxicillin with total saturation of PBPs 2 and 3 by cefotaxime

Figure 3

*PBP = Penicillin Binding Protein

Combination amoxicillin plus cefotaxime yields partial saturation of PBPs 4/5 and total saturation of PBPs 2/3
IX. Timeline of Dual β-lactam synergy evidence

1970's: gentamicin produced

1980's: gentamicin replaces streptomycin in βL/AG combo

1983: gentamicin resistance emerges

1984: Up to 81% of EIE isolates streptomycin resistant

1980's: gentamicin replaces streptomycin in βL/AG combo

1980's: gentamicin replaces streptomycin in βL/AG combo

1995: AHA guidelines recommend 4-6wk AG combination

1995: amoxicillin/cefotaxime synergy

1990's: HLAR increases precluding AG/βL synergy

1999: amoxicillin/cefotaxime synergy despite HLAR

2000's: Short course AG therapy equally efficacious

2005: AHA guidelines recommend 4-6 weeks AG combination
X.

Gavalda et al.\textsuperscript{28}

f. Published in Journal of Antimicrobial Chemotherapy 2003
g. Animal model of endocarditis
h. \textit{E. faecalis} without high-level aminoglycoside resistance

XI.

Gavalda et al.\textsuperscript{29}

i. Published in Annals of Internal Medicine 2007
j. 9 year multi-center non-randomized observational study
k. Both HLAR and non-HLAR strains of \textit{E. faecalis}

XII.

Fernandez-Hidalgo et al. \textsuperscript{30}

l. Published in Clinical Infectious Diseases 2013
m. 7 year observational non-randomized comparative cohort study
n. Ampicillin plus ceftriaxone v. ampicillin plus gentamicin
o. Both HLAR and non-HLAR strains

XIII.

Ceron et al. \textsuperscript{31}

p. Published in Journal of Antimicrobial Chemotherapy 2014
q. 5 year retrospective comparative study
r. Comparison of monotherapy v combination regimens
| Purpose | • Test the usefulness of ceftriaxone combined with ampicillin as an alternative to ampicillin plus gentamicin  
• Also to determine efficacy of ceftriaxone added to ampicillin/gentamicin combination |
| Design | • Pharmacokinetic in-vitro study |
| Patient Population | • Experimental endocarditis  
• “Human-like” pharmacokinetic model  
• *E. faecalis* without high-level aminoglycoside resistance |
| Outcomes | • Synergy between ampicillin, gentamicin and ceftriaxone  
  - Disc-diffusion method  
  - Time-kill synergy studies |
| Methods | • *E. faecalis* EF91 recovered from patient with endocarditis  
• Aortic endocarditis was induced in New Zealand rabbits with 1ml inoculum containing $10^{8}$ CFU of EF91  
• 3 day treatment protocol in human-like pharmacokinetic model  
  - Control – without treatment  
  - Ampicillin 2g every 4 hours  
  - Ampicillin 2g every 4 hours + gentamicin 1mg/kg every 8 hours  
  - Ampicillin 2g every 4 hours + ceftriaxone 2g every 12 hours  
  - Ampicillin 2g every 4 hours + ceftriaxone 2g every 12 hours + gentamicin 6mg/kg every 24 hours subcutaneously  
• 6 hours after completion of final antibiotic infusion colony counts in vegetation were determined |
| Statistics | • Vegetation bacterial concentrations compared using one-way analysis of variance  
• Each treatment group was compared to the control group and other treatment groups using Scheffe's test  
• P values <0.05 were considered significant |
| Results | • Combinations of ampicillin with gentamicin or ceftriaxone were more effective than ampicillin alone ($p<0.05$)  
• Synergistic effects were seen with ampicillin/gentamicin and ampicillin/ceftriaxone  
• Bacterial counts of vegetations were reduced in all treatment groups compared to controls  
• Ampicillin plus ceftriaxone was as effective as ampicillin plus gentamicin ($p=NS$)  
• Ampicillin combined with gentamicin and ceftriaxone was not superior to either combination of ampicillin plus gentamicin/ceftriaxone ($p=NS$) |
| Authors’ Conclusions | • Synergistic activity demonstrated between ampicillin and ceftriaxone  
• Combination of ampicillin plus ceftriaxone was as effective as ampicillin plus gentamicin administered in three daily doses  
• Combination of ampicillin plus ceftriaxone broadens the range of alternative therapy for treatment of enterococcal endocarditis |
| Strengths | • Ampicillin/ceftriaxone combination compared to gold standard (ampicillin/gentamicin)  
• EF91 isolate recovered from documented enterococcal endocarditis patient  
• Simulation of human serum pharmacokinetics – no data on validation of model |
| Weaknesses | • In-vitro data  
• Pharmacokinetic model for “human-like” antibiotic administrations  
• Non – HLAR isolates  
• Overall resistance to penicillin unknown |
| Take Home Points | • Combination of ampicillin/ceftriaxone as effective as ampicillin/gentamicin in-vitro  
• Definite synergy with dual β-lactam combination |
**Purpose**
- To evaluate the efficacy and safety of ampicillin plus ceftriaxone for treating endocarditis due to *E. faecalis* with and without HLAR

**Design**
- Observational, open-label, non-randomized, multicenter trial

**Patient Population**
- 43 patients with documented *E. faecalis* endocarditis from 13 centers in Spain
  - 21 HLAR *E. faecalis*
  - 22 non-HLAR *E. faecalis*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLAR E. faecalis</th>
<th>Non-HLAR E. faecalis</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>21 (49%)</td>
<td>22 (51%)</td>
<td>43</td>
</tr>
<tr>
<td>Age, y. (avg)</td>
<td>61.3</td>
<td>64.8</td>
<td>63</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>15 (71%)</td>
<td>13 (59%)</td>
<td>28 (65%)</td>
</tr>
<tr>
<td>F</td>
<td>6 (29%)</td>
<td>9 (41%)</td>
<td>15 (35%)</td>
</tr>
<tr>
<td>Underlying Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diabetes</td>
<td>4 (19%)</td>
<td>5 (23%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>- CKD</td>
<td>3 (15%)</td>
<td>5 (23%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Source of Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Community</td>
<td>13 (62%)</td>
<td>20 (91%)</td>
<td>33 (77%)</td>
</tr>
<tr>
<td>- Health-care</td>
<td>8 (38%)</td>
<td>2 (9%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Predisposing Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>8 (38%)</td>
<td>6 (27%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>- Identified</td>
<td>13 (62%)</td>
<td>16 (73%)</td>
<td>29 (67%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aortic</td>
<td>11 (53%)</td>
<td>14 (64%)</td>
<td>25 (58%)</td>
</tr>
<tr>
<td>- Mitral</td>
<td>6 (29%)</td>
<td>5 (23%)</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>Symptom Duration, d</td>
<td>30.7</td>
<td>28.9</td>
<td>29.8</td>
</tr>
</tbody>
</table>

**Outcomes**
- Duration of therapy, rates of adverse events, complications, surgical intervention and overall treatment failure

**Methods**
- Patients enrolled between 1995-2003
- Protocol amendment in 2000: include patients with non-HLAR enterococcal infection and renal failure or a risk for nephrotoxicity
- *E. faecalis* strains identified using API 20 STREP system and later confirmed in laboratory
- Treatment: ampicillin IV 2g every 4 hours + ceftriaxone IV 2g every 12 hours for 6 weeks (given in sequence over 30-60 minutes)
  - Cefotaxime 50 mg/kg every 4 hours was substituted in patients at risk for biliary toxicity

**Statistics**
- Compared continuous variables using the Mann-Whitney U test
- Compared proportions between groups using the χ² test
- All statistical tests were 2-tailed
- Threshold of statistical significance p<0.05

**Results**
- No patient developed nephrotoxicity
- No patient with HLAR suffered relapse at 3 month follow-up
- No patient who completed therapy had relapse
- Clinical and microbiological cure 100% at end of treatment and 3 month follow-up in the per protocol population
  - Clinical cure when all episodes analyzed
    - 71.4% (HLAR) and 72.7% (Non-HLAR) at end of therapy
    - 71.4% (HLAR) and 63.6% (Non-HLAR) at 3 months
- Overall treatment related mortality 28%
<table>
<thead>
<tr>
<th>Variable</th>
<th>HLAR E. faecalis</th>
<th>Non-HLAR E. faecalis</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Tx ≥42d Mean, d</td>
<td>13 (62%)</td>
<td>14 (64%)</td>
<td>27 (63%)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>20 (95%)</td>
<td>21 (95%)</td>
<td>41 (95%)</td>
</tr>
<tr>
<td>- Rash/Fever</td>
<td>0</td>
<td>1 (5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>- Leukopenia</td>
<td>1 (5%)</td>
<td>0</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Complications</td>
<td>9 (43%)*</td>
<td>16 (73%)</td>
<td>25 (58%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>3 (14%)</td>
<td>4 (18%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Failures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death During Treatment</td>
<td>6 (28%)</td>
<td>8 (37%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>- Death During F/U **</td>
<td>0</td>
<td>2 (9%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>- Relapse</td>
<td>0</td>
<td>2 (9%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>- ADR</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

*p=0.021; **1 patient who died during follow up also relapsed

**Authors’ Conclusions**

- Combination ampicillin/ceftriaxone broadens range of alternative therapies for HLAR/Non-HLAR but penicillin=susceptible enterococcal endocarditis
- Combination of ampicillin/ceftriaxone is effective therapy for HLAR E. faecalis
- Ampicillin/ceftriaxone is treatment of choice for endocarditis caused by HLAR E. faecalis

**Strengths**

- Efficacy of ampicillin/ceftriaxone combination in clinical setting
- Both HLAR/Non-HLAR
- Accounted for surgical intervention and compared overall complication rate

**Weaknesses**

- No comparator arm (ampicillin/gentamicin)
- All isolates penicillin susceptible
- Small sample size
- Overall mortality rate higher than previous studies (~20%)6,8,16,23

**Take Home Points**

- Ampicillin/ceftriaxone is a viable option for HLAR/Non-HLAR and PCN susceptible E. faecalis endocarditis
- Ampicillin/ceftriaxone is non-nephrotoxic and should be heavily considered in patients at risk for nephrotoxicity
- Spurred AHA guideline revision to include ampicillin/ceftriaxone as alternative for E. faecalis IE with HLAR to both streptomycin/gentamicin16
Purpose
• Compare the effectiveness of the ampicillin plus ceftriaxone (AC) and ampicillin plus gentamicin (AG) combinations for treating E. faecalis infective endocarditis (EFIE)

Design
• Observational, non-randomized, comparative multi-center cohort

Patient Population
• 291 episodes in 291 consecutive adult patients diagnosed with EFIE
  o 272 (94%) definite IE
  o 72 (25%) HLAR

<table>
<thead>
<tr>
<th>Variable</th>
<th>AC (n=159)</th>
<th>AG (N=87)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age, Y</td>
<td>70.4</td>
<td>69.8</td>
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</tr>
<tr>
<td>Male</td>
<td>114 (72%)</td>
<td>62 (72%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Definite IE</td>
<td>146 (92%)</td>
<td>84 (97%)</td>
<td>0.151</td>
</tr>
<tr>
<td>CCI, Median</td>
<td>2</td>
<td>2</td>
<td>0.053</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>53 (33%)</td>
<td>14 (16%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>29 (18%)</td>
<td>6 (7%)</td>
<td>0.015</td>
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<tr>
<td>HIV</td>
<td>2 (1%)</td>
<td>6 (7%)</td>
<td>0.017</td>
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<tr>
<td>Transplant</td>
<td>10 (6%)</td>
<td>0</td>
<td>0.04</td>
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<tr>
<td>Health-care Associated</td>
<td>93 (59%)</td>
<td>35 (40%)</td>
<td>0.006</td>
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<tr>
<td>Duration Of Symptoms, D</td>
<td>17</td>
<td>19</td>
<td>0.36</td>
</tr>
<tr>
<td>Type OfIE</td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>- Native Valve</td>
<td>98 (62%)</td>
<td>57 (66%)</td>
<td></td>
</tr>
<tr>
<td>- Prosthetic Valve</td>
<td>59 (37%)</td>
<td>30 (34%)</td>
<td></td>
</tr>
<tr>
<td>Source Of Infection</td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>- Unknown</td>
<td>49 (31%)</td>
<td>37 (43%)</td>
<td></td>
</tr>
<tr>
<td>- Urologic</td>
<td>53 (33%)</td>
<td>18 (21%)</td>
<td></td>
</tr>
<tr>
<td>- Catheter Associated</td>
<td>20 (13%)</td>
<td>12 (14%)</td>
<td></td>
</tr>
<tr>
<td>- Gastrointestinal</td>
<td>17 (11%)</td>
<td>10 (12%)</td>
<td></td>
</tr>
<tr>
<td>Vegetation Size, mm</td>
<td>10</td>
<td>10</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Outcomes
• Death during treatment
• Death during 3-month follow up
• Adverse events requiring treatment withdrawal
• Treatment failure requiring change of antibiotics
• Relapse

Methods
• 17 Spanish and 1 Italian hospital
• Adult patients with a diagnosis of EFIE treated during January 2005 - December 2011
• IE defined as definite or possible according to modified duke criteria
• Charlson comorbidity index used to stratify overall comorbidity at admission
• Indication for surgery established according to published guidelines
• Patient classified as received AC or AG if once etiology was known, a 4-6 week course was planned (AG=2 wk of gentamicin)
• Treatment
  o Ampicillin 2g every 4 hours (adjusted according to renal function)
  o Ceftriaxone 2g every 12 hours
  o Gentamicin 3mg/kg/day (adjusted according to renal function) in 1, 2 or 3 divided doses (discretion of attending physician)
• Trough levels monitored according to local protocols; target 0.5-1 mg/L for multi-dose administration
• Adverse effects of treatment groups were considered after excluding other potential causes
Statistics

- Quantitative variables were reported as median
- Qualitative variable were reported as percentages
- \( \chi^2 \) test used to compare categorical variables
- Student t test used for comparison of continuous variables
- Mann-Whitney test used for variables with non-normal distribution
- Differences were considered significant at p<0.05
- All outcomes were estimated using an intent to treat analysis
- All tests were 2 sided, with a 95% confidence interval

Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>AC (n=159)</th>
<th>AG (N=87)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration Of ABX, D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In Survivors</td>
<td>42</td>
<td>42</td>
<td>0.122</td>
</tr>
<tr>
<td>- Days To Surgery</td>
<td>11</td>
<td>9</td>
<td>0.34</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overall</td>
<td>14 (9%)</td>
<td>38 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Overall D/T W/D</td>
<td>2 (1%)</td>
<td>22 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- New Renal Failure</td>
<td>0</td>
<td>20 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Due To Ototoxicity</td>
<td>0</td>
<td>2 (2%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Any</td>
<td>120 (76%)</td>
<td>72 (83%)</td>
<td>0.187</td>
</tr>
<tr>
<td>- Heart Failure</td>
<td>87 (55%)</td>
<td>54 (62%)</td>
<td>0.27</td>
</tr>
<tr>
<td>- New Renal Failure</td>
<td>53 (33%)</td>
<td>40 (46%)</td>
<td>0.051</td>
</tr>
<tr>
<td>- Paravalvular</td>
<td>36 (23%)</td>
<td>22 (25%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Surgery Indicated</td>
<td>92 (58%)</td>
<td>54 (62%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Surgery Performed</td>
<td>53/92 (58%)</td>
<td>35/54 (65%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Reason For No Surgery, If Indicated</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>- High–Risk</td>
<td>12/39 (31%)</td>
<td>9/19 (47%)</td>
<td></td>
</tr>
<tr>
<td>- Critical Status</td>
<td>9/39 (23%)</td>
<td>4/19 (21%)</td>
<td></td>
</tr>
<tr>
<td>- Age</td>
<td>7/39 (18%)</td>
<td>1/19 (5%)</td>
<td></td>
</tr>
<tr>
<td>Surgery During Follow Up</td>
<td>4/117 (3%)</td>
<td>6/69 (9%)</td>
<td>0.094</td>
</tr>
<tr>
<td>In Hospital Death - Overall</td>
<td>42 (26%)</td>
<td>22 (25%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Failures</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Death During Therapy</td>
<td>35 (22%)</td>
<td>18 (21%)</td>
<td>0.81</td>
</tr>
<tr>
<td>- Death During Follow-Up</td>
<td>13 (8%)</td>
<td>6 (7%)</td>
<td>0.72</td>
</tr>
<tr>
<td>- Treatment Failure</td>
<td>2 (1%)</td>
<td>22 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- ADR Requiring W/D</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0.54</td>
</tr>
<tr>
<td>- Requiring ABX Change</td>
<td>3/124 (3%)</td>
<td>3/69 (4%)</td>
<td>0.67</td>
</tr>
<tr>
<td>- Relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Authors’ Conclusions

- AC appears as effective as AG for treating EFIE and can be used with virtually no risk of renal failure and regardless of HLAR status of E. faecalis

Strengths

- Actual patient data v. standard of care
- Both HLAR/non-HLAR in AC group with similar results to AG
- AC patients in poorer overall condition at baseline
- Assessed health-care association EFIE

Weaknesses

- Many patients didn’t complete entirety of gentamicin therapy; therapy decisions physician specific with only 60% gentamicin monitoring
- No data on β-lactam ADR
- Design: Non-inferiority/Superiority?

Take Home Points

- AC patients were poorer overall and had similar outcomes
- AG patients had increased rates of new onset renal failure, while AC did not despite worse renal function initially
Data presented affirms AC as option for EFIE in patients with specific characteristics


**Purpose**
- Analyze the effectiveness of daptomycin monotherapy against conventional therapy in enterococcal IE

**Design**
- Retrospective descriptive single-center study

**Patient Population**
- 32 patients with Enterococcal IE
- Included all patients >18 years old with a definite or possible enterococcal IE, treated with effective antimicrobial therapy >48 hours
- Excluded patients who started daptomycin (D) after >14 days of other antibiotic regimens and patients with polymicrobial IE

<table>
<thead>
<tr>
<th>Variable</th>
<th>D (n=6)</th>
<th>AC (n=21)</th>
<th>AG (n=5)</th>
<th>p</th>
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<tr>
<td>Age</td>
<td>76.7</td>
<td>71</td>
<td>65.2</td>
<td>0.18</td>
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<tr>
<td>Underlying Condition</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diabetes</td>
<td>2 (33%)</td>
<td>7 (33%)</td>
<td>1 (20%)</td>
<td>0.84</td>
</tr>
<tr>
<td>- Malignancy</td>
<td>1 (17%)</td>
<td>8 (38%)</td>
<td>0</td>
<td>0.18</td>
</tr>
<tr>
<td>- Renal Insufficiency</td>
<td>3 (50%)</td>
<td>10 (48%)</td>
<td>2 (40%)</td>
<td>0.60</td>
</tr>
<tr>
<td>- Immunosuppression</td>
<td>0</td>
<td>8 (38%)</td>
<td>1 (20%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Charlson Score</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0.69</td>
</tr>
<tr>
<td>Previous IE</td>
<td>0</td>
<td>4 (19%)</td>
<td>1 (20%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Definite IE</td>
<td>5 (83%)</td>
<td>20 (95%)</td>
<td>5 (100%)</td>
<td>0.46</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>5 (83%)</td>
<td>20 (95%)</td>
<td>4 (80%)</td>
<td>0.45</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>1 (17%)</td>
<td>0</td>
<td>1 (20%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**Outcomes**
- Days of bacteremia
- Complication (embolization, intracardiac abscess, vegetation size, heart failure, CNS event etc.)
- Length of hospital stay
- Mortality rate

**Methods**
- January 2007 – December 2011
- 6 patients with daptomycin monotherapy compared to 21 ampicillin/ceftriaxone patients and 5 ampicillin/gentamicin patients
- Daptomycin treated patients received ≥7 days of daptomycin (≥6 mg/kg/day) within the first 14 days after positive blood culture
  - Indications for daptomycin therapy were outpatient parenteral therapy and β-lactam allergy
- Ampicillin/ceftriaxone: Ampicillin 2g every 6 hours + ceftriaxone 2g every 12 hours
- Conventional group: Ampicillin 2g every 6 hours (or vancomycin 1g q12h) + gentamicin 1mg/kg every 8 hours

**Statistics**
- Continuous variables were compared using Students t test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables
- χ² or Fischer’s exact test was used to compare categorical variables
- All tests of significance were 2-tailed
- Differences were significant for p values <0.05

**Results**
- None of the daptomycin treated patients had previous treatment failure
- All strains were susceptible to daptomycin
- Mean administered dose of daptomycin 8.5 mg/kg/day (range:6-10 mg/kg/day)
- Daptomycin treated patients had a longer duration of bacteremia, more complications and required an antibiotic regimen change more frequently than the ampicillin/ceftriaxone and gentamicin groups
- All patients requiring therapy change were switched to ampicillin/ceftriaxone combination
Martinez, OJ

- No differences in rate of adverse events related to antimicrobial therapy, median duration of hospital stay or mortality between groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>D (n=6)</th>
<th>AC (n=21)</th>
<th>AG (n=5)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration Of Bacteremia, D</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complication Rate</td>
<td>5 (83%)</td>
<td>3 (14%)</td>
<td>1 (20%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Change In Antibiotic Therapy</td>
<td>4 (67%)</td>
<td>0</td>
<td>1 (20%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Surgery Performed</td>
<td>3 (50%)</td>
<td>4 (19%)</td>
<td>4 (80%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>0</td>
<td>0</td>
<td>1 (20%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospital Stay, D</td>
<td>43</td>
<td>32</td>
<td>45</td>
<td>0.83</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (17%)</td>
<td>9 (43%)</td>
<td>2 (49%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Authors’ Conclusions
- Daptomycin treated patients more frequently required a therapeutic change due to worse microbiological and clinical response, although mortality was not increased
- Findings do not support the use of daptomycin as a single therapy in the treatment of EIE

Strengths
- Compared daptomycin monotherapy versus current conventional therapies
- Included both *E. faecalis* and *E. faecium*
- Assessed duration of bacteremia, change in therapy and included surgical intervention

Weaknesses
- Small sample size
- Single center
- No data on aminoglycoside serum monitoring
- Ampicillin 2g every 6 hours instead of every 4 hours
- Trial not specifically designed to compare ampicillin/ceftriaxone to ampicillin/gentamicin

Take Home Points
- Authors included ampicillin/ceftriaxone as a comparator arm
- Ampicillin/ceftriaxone gaining recognition as viable option
- Ampicillin/ceftriaxone as effective as conventional therapy and superior to daptomycin monotherapy
CONCLUSIONS

XIV. Conclusions
   a. The clinical picture of EFIE has changed significantly since the dawn of the antibiotic era
   b. Susceptibility testing and the utilization of early surgical intervention are paramount to effectively treating enterococcal endocarditis patients
   c. The combination of ampicillin plus ceftriaxone has documented synergistic activity in-vitro as well as efficacy in clinical isolates
   d. Ampicillin plus ceftriaxone is less nephrotoxic than conventional therapy and is equally efficacious in cases of high level and non-aminoglycoside resistant *E. faecalis* endocarditis cases

XV. Future directions
   a. Use of β-lactam and aminoglycoside combinations should be cautioned as increasing rates of aminoglycoside resistance precludes their synergistic actions
   b. Need for larger trials with stronger methodology is hampered by low prevalence of EFIE
   c. Calls to further research in this area have gone unanswered
   d. No plans for revision of current guideline
   e. Researchers have already begun to view ampicillin/ceftriaxone as a comparative regimen going forward

XVI. Recommendations
   s. Ampicillin plus ceftriaxone should be considered as an alternative to conventional therapy in patients with *E. faecalis* endocarditis
   t. Patients presenting with renal dysfunction at baseline should be strongly considered for dual β-lactam therapy
   u. Patients in which a long hospital course is not ideal can consider ampicillin plus ceftriaxone due to the decreased burden of administration versus conventional therapy
References:

33. Martinez O. Phone call to AHA office in Dallas, Texas. 2014.
Appendix A

<table>
<thead>
<tr>
<th><strong>Definitions</strong></th>
<th><strong>IE</strong></th>
<th>Infective Endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EIE</strong></td>
<td>Enterococcal Infective Endocarditis</td>
<td></td>
</tr>
<tr>
<td><strong>EFIE</strong></td>
<td>E. faecalis Infective Endocarditis</td>
<td></td>
</tr>
<tr>
<td><strong>HLAR</strong></td>
<td>High Level Aminoglycoside Resistance</td>
<td></td>
</tr>
<tr>
<td><strong>AC</strong></td>
<td>Ampicillin plus ceftriaxone</td>
<td></td>
</tr>
<tr>
<td><strong>AG</strong></td>
<td>Ampicillin plus gentamicin</td>
<td></td>
</tr>
<tr>
<td><strong>βL</strong></td>
<td>β-lactam antibiotic</td>
<td></td>
</tr>
<tr>
<td><strong>ABX</strong></td>
<td>Antibiotic</td>
<td></td>
</tr>
<tr>
<td><strong>Disc Diffusion Method</strong></td>
<td>Test for antimicrobial susceptibility utilizing antibiotic impregnated wafers</td>
<td></td>
</tr>
<tr>
<td><strong>Time Kill Synergy Study</strong></td>
<td>Antibiotics are incorporated into broth tubes that contain organisms and are then are mapped according to “time-kill”. Provides</td>
<td></td>
</tr>
<tr>
<td><strong>Scheffee’s Test</strong></td>
<td>Statistical method used to adjust significance levels to account for multiple comparisons when performing linear regression analysis. Decreases variance in analysis</td>
<td></td>
</tr>
<tr>
<td><strong>API 20 STREP</strong></td>
<td>Provides rapid identification of enterococci within 24 hours.</td>
<td></td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index</strong></td>
<td>Assessment of a patient's status that determines if they will live long enough to benefit from a specific intervention</td>
<td></td>
</tr>
</tbody>
</table>

Appendix B

- Predisposition/Congenital Abnormality
- Altered Endothelial Surface
- Platelet/fibrin deposition
- Bacterial Adherence
- Organism reproduction
- Destruction of endothelial tissue
- Fibrosis/valvular insufficiency
- Embolization/Septic emboli
- Infarction/Death

Appendix C

- B-lactam monotherapy not fully bactericidal against *enterococcus* → Aminoglycoside monotherapy yields minimal intracellular uptake → Combination facilitates aminoglycoside uptake and subsequent bactericidal effect

![Diagram](https://via.placeholder.com/150)
### Appendix D

Amoxicillin partially saturates PBP 4/5

Ceftotaxime occupies PBP 2/3 at low concentrations and 1/4/5 at higher concentrations

Combination yields partial saturation of PBP 4/5 and total saturation of PBP 2/3

### Appendix E

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td>PK In-vitro</td>
<td>Observational</td>
<td>Observational cohort</td>
<td>Retrospective, descriptive</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>AC synergy</td>
<td>Use of AC in EFIE therapy</td>
<td>Compare AC against AG</td>
<td>Compare daptomycin against conventional combinations</td>
</tr>
<tr>
<td><strong># Patients</strong></td>
<td>1 (EF91 clinical isolate)</td>
<td>43</td>
<td>291</td>
<td>32</td>
</tr>
<tr>
<td><strong>E. faecalis</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>E. faecium</strong></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Ampicillin/gentamicin</strong></td>
<td>✓</td>
<td>✓ (n=87)</td>
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<td><strong>Ampicillin/ceftriaxone</strong></td>
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</tr>
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<td><strong>Daptomycin</strong></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>HLAR</strong></td>
<td>✓ (n=21)</td>
<td>✓ (n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>✓ (No Δ)</td>
<td>✓ (No Δ)</td>
<td>✓ (No Δ)</td>
<td></td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>✓ (4%)</td>
<td>✓ (No Δ)</td>
<td>AC 3%; AG 4%</td>
<td></td>
</tr>
<tr>
<td><strong>ADR</strong></td>
<td>✓ (&lt;2%)</td>
<td>✓ (AG 44%; AC 9%)</td>
<td>✓ D=AC &gt;&gt; AG (20%)</td>
<td></td>
</tr>
</tbody>
</table>