A New Era for Treating *Enterococcus Faecalis* Endocarditis:

Ampicillin plus Short-Course Gentamicin or Ampicillin plus Ceftriaxone;

That is the Question!

**Running title:** Miro et al.; New antibiotic treatments for E. faecalis endocarditis

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Enterococci are the third most common etiologic agent of infective endocarditis worldwide after staphylococci and streptococci and cause 10-15% of cases\(^1\). Enterococcal infections are increasingly relevant, especially among the elderly and patients with comorbid conditions in the healthcare setting\(^2,3\). Approximately 90% of cases of enterococcal endocarditis are caused by \textit{Enterococcus faecalis}, with less than 5% caused by \textit{Enterococcus faecium}\(^2,3\). The morbidity and mortality of enterococcal endocarditis is high. The percentage of patients requiring cardiac surgery (42%) and the 1-year mortality rate (29%) have remained almost unchanged for the last 30 years, and recent data show that they may even be increasing\(^3\).

This worrying picture is worsened by the increase in resistance to classic antimicrobials, especially to high-level aminoglycoside (HLAR). However, American Heart Association (AHA) guidelines\(^4\) have not modified their antibiotic recommendations on non-HLAR strains for almost 6 decades, and no randomized clinical trials (RCT) support current evidence. Since the empirical use of ampicillin+streptomycin has proven efficacious\(^5\) and synergistic (increased cell membrane permeability to aminoglycosides induced by betalactams \textit{in vitro} with enterococci)\(^6\), the efficacy of combining a betalactam with an aminoglycoside is unquestionable. The latest AHA guidelines maintain penicillin or ampicillin (or vancomycin in case of allergy to betalactams) plus gentamicin as the combination of choice for \textit{E. faecalis} infective endocarditis (EFIE) caused by non-HLAR strains\(^4\). Recommendations on length of treatment have also remained unchanged since the 1980s\(^7\), namely, 4 weeks for uncomplicated native-valve endocarditis and 6 weeks for prosthetic-valve endocarditis (PVE) and patients with a >3-month history of symptoms before diagnosis\(^4\). The gentamicin dose schedule (3 mg/kg per 24 h IV/IM in 3 equally spaced doses) has also remained unchanged for 2 decades.

In this issue of \textit{Circulation}, Dahl et al\(^8\) reported on the efficacy and safety of
ampicillin+short-course gentamicin for treating non-HLAR EFIE in Denmark. The rationale of the study relies on the good results reported in 2002 in Sweden by Olaison and Schadewitz, who performed a 5-year prospective study including 93 cases of EFIE. Clinical cure was achieved in 75 episodes (81%) that had been treated with a median 2-week course of aminoglycosides. Mortality was 16% and the relapse rate 3%, although neither was associated with the shortened course of therapy. These results led to a change in the Danish Society of Cardiology guidelines in 2007, when the course of gentamicin was reduced from 4-6 weeks to 2 weeks in order to reduce nephrotoxicity caused by prolonged treatment with aminoglycosides. However, the study by Olaison and Schadewitz is limited by the lack of microbiological data (i.e. percentage of HLAR), the omission of the type of aminoglycosides used, the low percentage of patients with symptoms for >3 months (only 5%), the short follow-up (53% at 3 months), and the fact that no analysis of antimicrobial-associated adverse events is provided. The study by Dahl et al overcome these limitations. Hypothesizing that outcomes would not differ between short- and standard-course gentamicin in EFIE, the authors performed a pilot prospective cohort study with a historical control group (Table 1). Furthermore, given that almost all patients had been treated with a short course of gentamicin since the national guidelines were modified in 2007, the authors were able to compare 41 cases of left-sided non-HLAR EFIE treated during the 5 years before and 43 cases treated during the 5 years after the modifications. Baseline characteristics (including Charlson comorbidity index, duration of symptoms, and rates of PVE) were similar in both groups. Mean duration of treatment with gentamicin was 28 and 14 days, respectively. Notably, renal function, expressed using glomerular filtration rate (GFR), was also similar in both groups before initiation of treatment. All patients received gentamicin 3 mg/kg, trough levels were monitored in all cases, and dose schedule did not differ significantly between the 2
groups (QD in 82% and 93%, respectively). No statistically significant differences were detected in the primary endpoint, event-free 1-year survival (66% vs. 69%; \( P=0.75 \)), even after stratification by PVE. No differences were found regarding heart failure, stroke or other embolisms, in-hospital surgery, in-hospital mortality, or relapses. Nonetheless, loss of renal function was less frequent in the group receiving short-course gentamicin (\( P=0.008 \)). No analysis of other adverse events secondary to antimicrobial treatment was performed.

This study provides novel data on non-HLAR EFIE and aminoglycoside use. First, it demonstrates that 2 weeks of gentamicin was as efficacious as and less nephrotoxic than 4-6 weeks. Remarkably, short-course gentamicin was also safe and efficacious for *E. faecalis* PVE. Second, it shows that QD gentamicin was clinically efficacious. AHA guidelines recommend a schedule comprising 3 equally spaced doses (TID) of gentamicin\(^4\), and European Society of Cardiology (ESC) guidelines (based on experimental data) recommend a BID or TID regimen\(^11\). However, these findings are open to debate. The study by Hessen et al\(^12\) showed that the post-antibiotic effect of QD gentamicin did not achieve bactericidal concentrations in vegetations of rats with EFIE treated with penicillin and gentamicin; the authors suggested shortening the dosing interval in order to maintain antibiotic levels over the minimum inhibitory concentration. Subsequent results are consistent with these findings. However, using a human-like pharmacokinetic model, Gavaldà et al\(^13\) found that the therapeutic efficacy of ampicillin+gentamicin was not significantly affected by the gentamicin dosing interval, with QD dosing similar to TID dosing\(^13\). The study by Dahl et al\(^8\) is the first to provide data from a large number of patients treated with a QD gentamicin schedule. Seventy-two (86%) of the 84 patients received a QD regimen, only 10 received TID, and 2 BID, with no association between poor outcome and dosing interval. Third, the authors provide evidence that nephrotoxicity was
associated with the duration of gentamicin therapy, because at 2 weeks the decrease in GFR was very small and similar in both cohorts \( (P=0.65) \). However, at discharge, patients who received the standard gentamicin course had a significantly greater decrease in GFR (11 vs. 1 ml/min, \( P=0.008 \)). Therefore, this finding is especially relevant, since the typical EFIE patient is older, with high rates of chronic renal failure (CRF) and a high risk of rapid renal impairment. The use of GFR as a measure of renal function is a wise choice, since it accurately reflects the impact of treatment on kidney integrity, unlike the widely used creatinine value, which can be easily misinterpreted depending on age, muscle mass and other factors. Moreover, avoiding the bias of selecting the duration of the course of gentamicin according to individual baseline renal function yielded more robust results and led to clear conclusions, namely, the course of gentamicin in non-HLAR EFIE should be shortened to avoid nephrotoxicity, especially in elderly patients with CRF, who are the main target when treating EFIE and the most susceptible to developing aminoglycoside-induced toxicity. On the other hand, this new antibiotic regimen cannot be extended to EFIE caused by HLAR strains, which have a current prevalence of 22% in North America and 38% in the rest of the world\(^3\).

In a study carried out in Spain and Italy, Fernández-Hidalgo et al\(^14\) investigated the efficacy and safety of ampicillin+ceftriaxone to treat EFIE. This study was inspired by the revealing finding that a double beta-lactam combination was synergistic \textit{in vitro} through partial saturation of penicillin-binding proteins (PBPs) 4 and 5 by amoxicillin and total saturation of PBPs 2 and 3 by cefotaxime\(^15\). The results prompted animal models, which demonstrated synergy of ampicillin+ceftriaxone in experimental EFIE for both HLAR strains\(^16\) and non-HLAR strains\(^17\). Shortly afterwards, Gavaldà et al\(^18\) proved the preliminary efficacy of the combination in a multicenter, open-label study that evaluated 43 patients with EFIE (49% with HLAR strains
and 51% non-HLAR strains) treated with ampicillin (2 g/4 h) and ceftriaxone (2 g/12 h).\(^{18}\) Clinical cure rates were 71% and 73%, respectively, with 5% relapses. The study by Fernández-Hidalgo et al\(^{14}\) was an observational, nonrandomized, comparative multicenter cohort study including 159 patients treated with ampicillin+ceftriaxone (31% HLAR strains) and 87 patients treated with ampicillin+gentamicin (all non-HLAR strains) (Table 1). Gentamicin was administered for as long as ampicillin in 31 patients (36%); it was stopped after a median (IQR) of 23 (14-34) days in 34 patients with no adverse events. In 20 of the 22 patients in whom gentamicin was withdrawn because of adverse events (20 patients experienced renal failure), the median length of treatment was 14-15 days. The gentamicin schedule was QD, BID, TID, or unknown in 43%, 7%, 43%, and 7%, respectively. Overall, no differences were found between the 2 groups regarding treatment failure, mortality during treatment or at 3 months of follow-up, and relapses. However, a higher proportion of patients receiving ampicillin+gentamicin switched or stopped gentamicin owing to renal failure (0 vs. 23%; \(P<0.001\)). At baseline, more patients in the ampicillin+ceftriaxone group had CRF (\(P=0.004\)), and although an outcome analysis based on the presence of HLAR was not performed, ampicillin+ceftriaxone proved effective in both strains and was globally safer than ampicillin+gentamicin for 4-6 weeks. AHA\(^4\) and ESC\(^{11}\) guidelines consider ampicillin+ceftriaxone administered for at least 8 weeks a potential antibiotic therapy for EFIE with HLAR to both streptomycin and gentamicin; however, neither the AHA nor the ESC considers this combination the treatment of choice for non-HLAR EFIE. We believe the study by Fernández-Hidalgo et al confirms that this combination given for a median of 6 weeks is an effective therapy for both HLAR and non-HLAR EFIE and that it was safer than 4 to 6 weeks of ampicillin+gentamicin, although we do not know if the rate of discontinuation of gentamicin would have been the same with only 2 weeks of gentamicin therapy, especially
considering that the median length of therapy with gentamicin in those patients who developed renal failure was 2 weeks. This study does not clarify if 4 weeks of ampicillin+ceftriaxone would be effective against uncomplicated native valve EFIE.

Both studies are subject to limitations. The most important is they are not randomized controlled trials. The study by Dahl et al\(^8\) is also limited by the small sample size of both cohorts and insufficient power; therefore, the results need to be interpreted with caution. In the study by Fernández-Hidalgo et al\(^{14}\), most cases were retrospectively collected, with the consequent potential biases in the choice of treatment combination, which depends on the existence of baseline CRF, and in when antibiotic therapy was stopped and switched in those patients on gentamicin who developed renal failure. In 10 patients, gentamicin was switched to ceftriaxone after a median (IQR) length of 15\(^7\)-17 days. In addition, the gentamicin schedule was not the same for all patients, and renal impairment was not assessed using GFR. In the study by Dahl et al, the exclusion of 5 patients undergoing hemodialysis could represent another bias, since this is a classic risk factor for EFIE, and no adverse events other than renal failure secondary to aminoglycoside treatment were assessed. Both studies are affected by referral bias, which is remarkable in the study by Fernández-Hidalgo et al, with an initial indication for cardiac surgery in 60% of cases. In addition, low numbers of patients with more than 3 months of symptoms might also be considered a limitation, although this might only reflect a higher clinical suspicion of IE resulting in an earlier diagnosis. Finally, the potential risk of colonization or superinfection by drug-resistant bacteria was not assessed. It is well known that prolonged therapy with cephalosporin is a risk factor for infection by vancomycin-resistant enterococci or \textit{Clostridium difficile}\(^{19}\).

In conclusion, both publications make an enormous contribution to improving the
efficacy and safety of treatment of EFIE. In patients with EFIE that is highly resistant to both streptomycin and gentamicin, ampicillin+ceftriaxone for 6 weeks should be the regimen of choice. In the case of patients with non-HLAR EFIE, there are 2 options: if treatment with ampicillin+gentamicin is chosen, gentamicin can be shortened to 2 weeks and simplified to QD dosing in order to avoid nephrotoxicity; conversely, ampicillin+ceftriaxone is also very safe and effective. Unfortunately, efforts to perform a multinational randomized controlled trial comparing ampicillin+short-course gentamicin with ampicillin+ceftriaxone in Europe through different FP7-HEALTH-2011/2012 calls (AMPICEF, ACEPPE, and TOTEM proposals) have failed 3 times (Pierre Tattevin, personal communication). Maybe it is time for American physicians to address this problem and resolve the dilemma: short-course gentamicin or ceftriaxone?

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Conflict of Interest Disclosures: None.

References:


Table 1. Main clinical characteristics and outcomes of the studies by Dahl et al^8^ and Fernández-Hidalgo et al^14^

<table>
<thead>
<tr>
<th>Country (n sites)</th>
<th>Dahl et al 2002-2006 Denmark (2)</th>
<th>Fernández-Hidalgo et al 2005-2011 Spain (17) and Italy (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study period</td>
<td>2002-2006</td>
<td>2007-2011</td>
</tr>
<tr>
<td>Antibiotic regimen</td>
<td>Ampicillin+gentamicin*</td>
<td>Ampicillin+ceftriaxone** Ampicillin+gentamicin*</td>
</tr>
<tr>
<td>No. of patients</td>
<td>41</td>
<td>159</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>70 (12) ¶</td>
<td>70 (11) ¶</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>32 (78) ¶</td>
<td>114 (72)</td>
</tr>
<tr>
<td>Charlson comorbidity score, median (IQR)</td>
<td>1.8 (1.9) ¶</td>
<td>2 (2-4)</td>
</tr>
<tr>
<td>Chronic renal impairment, n (%)</td>
<td>7 (17) ¶</td>
<td>53 (33)</td>
</tr>
<tr>
<td>Hemodialysis, n (%)</td>
<td>Excluded ¶</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Duration of symptoms (days), median (IQR)</td>
<td>20 (14-32) ¶</td>
<td>17 (5-44)</td>
</tr>
<tr>
<td>Type of valve, n (%)</td>
<td>- Native valve</td>
<td>- Native valve</td>
</tr>
<tr>
<td></td>
<td>- Prosthetic valve</td>
<td>- Prosthetic valve</td>
</tr>
<tr>
<td></td>
<td>- Pacemaker</td>
<td>- Pacemaker</td>
</tr>
<tr>
<td>Perivalvular abscess, n (%)</td>
<td>8 (20) ¶</td>
<td>36 (23)</td>
</tr>
<tr>
<td>HLA RIE, n (%)</td>
<td>Excluded ¶</td>
<td>51 (32)</td>
</tr>
<tr>
<td>Duration of antimicrobial treatment (days, in survivors) median (IQR)</td>
<td>ND</td>
<td>42 (39-46)</td>
</tr>
<tr>
<td>Duration of gentamicin (days)</td>
<td>28 (18-42) ¶</td>
<td>NA</td>
</tr>
<tr>
<td>Gentamicin QD, n (%)</td>
<td>32 (80) ¶</td>
<td>37 (43)</td>
</tr>
<tr>
<td>Duration of hospital stay (days), median (IQR)</td>
<td>42 (35-51) ¶</td>
<td>ND</td>
</tr>
<tr>
<td>Adverse events leading to treatment discontinuation</td>
<td>- Renal failure, n (%)</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>- Other ¶</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>In-hospital surgery, n (%)</td>
<td>15 (37)</td>
</tr>
<tr>
<td></td>
<td>In-hospital mortality, n (%)</td>
<td>4 (10)</td>
</tr>
<tr>
<td></td>
<td>Relapses (in survivors), n (%)</td>
<td>3/41 (7)</td>
</tr>
</tbody>
</table>

ND = No data; NA = Not applicable. * All patients were treated with gentamicin 3 mg/kg (up to 240 mg/day) administered IV 1-3 times daily at the discretion of the treating physician and adjusted according to renal function when necessary. ** Ceftriaxone was given at 2 g/12 h IV with ampicillin 2 g/4h IV (adjusted according to renal function when necessary) for 6 weeks. ¶ Mean (SD); ¶¶ Rash/fever and leukopenia in 1 case each in the ampicillin+ceftriaxone group; vestibular toxicity in 2 cases in the ampicillin+gentamicin group.
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