Brief Communication: Treatment of *Enterococcus faecalis* Endocarditis with Ampicillin plus Ceftriaxone

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**Background:** High-level aminoglycoside resistance (HLAR) that precludes bactericidal synergism with penicillins or glycopeptides and nephrotoxicity related to aminoglycoside treatment are major problems in treating *Enterococcus faecalis* endocarditis.

**Objective:** 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, nonrandomized, multicenter clinical trial.

**Setting:** 13 centers in Spain.

**Patients:** 21 patients with HLAR *E. faecalis* endocarditis and 22 patients with non-HLAR *E. faecalis* endocarditis. All were at risk for nephrotoxicity related to aminoglycoside use.

**Intervention:** 6-week course of intravenous ampicillin, 2 g every 4 hours, plus intravenous ceftriaxone, 2 g every 12 hours.

**Measurements:** Clinical and microbiological outcomes.

The American Heart Association recommends 4 to 6 weeks of penicillin or ampicillin plus an aminoglycoside for treating enterococcal endocarditis (1). Since the first reports in the late 1970s of *Enterococcus faecalis* clinical isolates with high-level aminoglycoside resistance (HLAR) (2), the number of infections caused by HLAR strains has been increasing worldwide (3–8). High-level aminoglycoside resistance precludes bactericidal synergism with penicillins or glycopeptides (3, 5, 6, 9, 10).

In an experimental endocarditis model using human-like antimicrobial pharmacokinetics, our group found in vitro and in vivo synergism against HLAR *E. faecalis* with combined ampicillin and ceftriaxone (3). The combination was as effective as ampicillin plus gentamicin for treating experimental endocarditis due to non-HLAR *E. faecalis* (12). In this observational, multicenter, open-label clinical trial, we aimed to evaluate the efficacy of treatment with ampicillin, 2 g every 4 hours, plus ceftriaxone, 2 g every 12 hours, in patients with endocarditis caused by *E. faecalis* with or without HLAR.

**Methods**

The institutional review boards of the participating institutions approved the study. Patients were eligible if they had definite endocarditis due to HLAR *E. faecalis* (highly resistant to gentamicin and streptomycin); were susceptible to ampicillin (minimal inhibitory concentration, 1 to 4 μg/mL) as described elsewhere (11), defined according to the modified Duke criteria (13); and provided written informed consent. Patients were consecutively enrolled between 1995 and 2003. In January 2000, a protocol amendment was approved to include patients with non-HLAR enterococcal infection and renal failure or a risk for nephrotoxicity. We enrolled a total of 43 patients from 13 centers throughout Spain. Data were previously presented in part elsewhere (14).

We identified *E. faecalis* strains by using the API 20 STREP system (bioMérieux, La Balme-les-Grottes, France) and later confirmed them according to the criteria recommended by Facklam and Collins (15) in a reference laboratory.

Patients received intravenous ampicillin, 2 g every 4 hours, plus intravenous ceftriaxone, 2 g every 12 hours, for 6 weeks. Ampicillin and ceftriaxone were both infused over

**Results:** The clinical cure rate at 3 months was 67.4% (29 of 43 patients) among all episodes. During treatment, 28.6% of patients with HLAR *E. faecalis* endocarditis and 18.2% of patients with non-HLAR *E. faecalis* endocarditis died of infection-related causes. The rate of clinical and microbiological cure in patients who completed the protocol was 100% in the HLAR *E. faecalis* endocarditis group. No episodes of breakthrough bacteremia occurred, although there were 2 relapses in the non-HLAR *E. faecalis* endocarditis group. Treatment was withdrawn in 1 case because of fever and skin rash.

**Limitations:** The study had a small sample and was observational.

**Conclusion:** The combination of ampicillin and ceftriaxone is effective and safe for treating HLAR *E. faecalis* endocarditis and could be a reasonable alternative for patients with non-HLAR *E. faecalis* endocarditis who are at increased risk for nephrotoxicity.


For author affiliations, see end of text.

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30 to 60 minutes, with ceftriaxone given just after the ampicillin infusion. In patients at risk for biliary toxicity due to ceftriaxone (2 cases), ceftaxime was allowed at a dosage of 50 mg/kg of body weight every 4 hours.

Patients were clinically assessed daily during their hospital stay. At least 1 follow-up visit took place 3 months after completion of therapy. Blood cultures were performed between 1 and 2 weeks after therapy was started, at the end of therapy, and at 3 months after therapy was completed.

We defined relapse as a new episode of endocarditis caused by the same strain during follow-up. We defined clinical cure as the resolution of the clinical findings of endocarditis with no evidence of active endocarditis at both the end of treatment and the 3-month follow-up visit.

We performed ampicillin plus ceftriaxone synergy studies in 16 HLAR E. faecalis strains (minimal inhibitory concentration of gentamicin >500 μg/mL) and in 12 non-HLAR E. faecalis strains. We performed time–kill synergy studies according to the method of Sahm and Torres (16). We defined antimicrobial synergism as a decrease of more than 2 log_{10} colony-forming units/mL between the combination and its most active agent alone after 24 hours.

We compared continuous variables between the 2 groups by using the Mann–Whitney U test and proportions between the 2 groups by using the chi-square test. All statistical tests were 2-tailed, and the threshold of statistical significance was a P value less than 0.05. We performed all statistical analyses with SPSS software, version 12.0 (SPSS Inc., Chicago, Illinois).

No outside funding was received for this study.

RESULTS

Table 1 shows the demographic characteristics of patients and clinical features of the infectious endocarditis episodes. Among the patients with endocarditis due to HLAR E. faecalis, 1 was 6 months of age, 10 (47.6%) were older than 65 years of age, and 7 (31.8%) were older than 70 years of age. Thirteen patients had native valve endocarditis, and 8 patients had prosthetic valve endocarditis. The aortic valve was most frequently affected (50%), and 38% of patients had no predisposing factor. Seven and 14 cases had vegetations on transthoracic echocardiography and on transesophageal echocardiography, respectively.

Table 2 shows the treatment features, outcome, and follow-up of infectious endocarditis episodes due to HLAR and non-HLAR E. faecalis. Among the patients with HLAR E. faecalis endocarditis, all who survived the endocarditis episode were treated for at least 1 month. One patient developed leukopenia, but treatment was maintained. No patient showed nephrotoxicity. Nine of 21 patients developed complicated endocarditis, with heart failure being the most frequent complication (5 cases). Surgery was not performed because of poor clinical status in 3 of 5 patients (age 72, 78, and 82 years) and was not considered in another episode. Three patients had surgery plus medical treatment. Seven patients died during therapy on mean treatment day 25 (range, 9 to 42 days); 1 of these deaths was not related to the endocarditis episode (death due to aspiration pneumonia). Six of the patients who died were older than 70 years of age. Blood cultures taken just before death were negative in all cases. Three of 8 (37.5%) patients with prosthetic valves died during the study, compared with 5 of 13 (38.5%) patients with native valves (P = 0.97).

Thirteen patients completed the treatment protocol. Eleven of these patients were cured with medical treatment alone, and 1 patient who had a pseudoaneurysm was cured with both medical treatment and surgery. One patient died on day 30 after treatment because of complications related to AIDS. No patient with HLAR E. faecalis endocarditis had relapse after 3 months of follow-up.

Two treatment failures occurred in patients with non-HLAR E. faecalis endocarditis that were diagnosed as relapses. One patient was erroneously treated with ampicillin at the study protocol dosage plus 2 g of ceftriaxone daily instead of 2 g every 12 hours, and only for 28 days. Twenty days after completing treatment, the patient returned to the hospital because of fever, and blood culture was again positive for E. faecalis. Re-treatment with ampicillin plus ceftriaxone, 2 g every 12 hours, resulted in cure with no evidence of relapse after 2 years of follow-up. The other patient was a 72-year-old man with a prosthetic aortic valve and a Dacron graft in the ascending aorta. He had death was not related to the endocarditis episode (death due to aspiration pneumonia). Six of the patients who died were older than 70 years of age. Blood cultures taken just before death were negative in all cases. Three of 8 (37.5%) patients with prosthetic valves died during the study, compared with 5 of 13 (38.5%) patients with native valves (P = 0.97).

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prosthetic aortic valve endocarditis, which was treated with ampicillin, 2 g every 4 hours, plus ceftriaxone, 2 g every 12 hours, for 42 days. He returned to the hospital 21 days after completing treatment with a cerebral hemorrhage that resulted in death. Blood cultures at this time were again positive for *E. faecalis*.

The clinical and microbiological cure rate was 100% at the end of treatment and at 3 months in patients who completed the protocol in the HLAR enterococcal endocarditis group. However, when we analyzed all enterococcal endocarditis episodes, rates were 71.4% and 72.7% at the end of treatment in the HLAR and non-HLAR enterococcal endocarditis groups, respectively, and 71.4% and 63.6% at 3 months (Figure).

The in vitro studies showed synergism of the treatment combination in the 28 strains tested.

**DISCUSSION**

The combination of ampicillin plus ceftriaxone broadens the range of alternative therapies for treating HLAR and non-HLAR but penicillin-susceptible enterococcal endocarditis. In previous studies, our group demonstrated the efficacy of this combination for treating experimental endocarditis due to these strains (11, 12). To date, no effective medical treatment for these patients are known, although the American Heart Association has recommended (strength of recommendation IIbC) ampicillin plus ceftri-
axone for native or prosthetic valve endocarditis caused by strains resistant to penicillin, aminoglycosides, and vancomycin (on the basis of our preliminary report in 20 patients [13 with HLAR endocarditis] [14] and other reports) plus surgical excision of infected valves when required (1). Two new drugs with activity against multidrug-resistant, gram-positive cocci have been recently approved, but quinupristin–dalfopristin is not active against \textit{E. faecalis} and the experience with linezolid is scarce and controversial in patients with \textit{E. faecalis} endocarditis (17, 18).

Our results show that the combination of ampicillin plus ceftriaxone or cefotaxime is effective therapy for endocarditis due to HLAR \textit{E. faecalis}. Among the 21 cases included, 11 were cured with the antibiotic combination alone and 3 that required valve replacement because of endocarditis-related complications had negative valve cultures. The treatment-related mortality rate was 28.6%, which is similar to that in other enterococcal endocarditis series (8, 19–22). Deaths were due to endocarditis-related complications in 6 cases (4 heart failures and 2 peripheral embolisms) and to the underlying disease in 1 case. Blood cultures before death were negative in all cases. No patient who completed therapy had relapse. On the basis of our results, we believe that combined treatment with ampicillin and ceftriaxone at a dosage of 2 g every 12 hours may be the treatment of choice for endocarditis caused by HLAR \textit{E. faecalis}.

Toxicity resulting from aminoglycosides depends mainly on the duration of treatment, the age of the patient, and the total amount of aminoglycoside administered. Because enterococcal endocarditis generally occurs in older individuals, older patients would benefit from less-toxic therapy. The results obtained in our small cohort of patients with non-HLAR \textit{E. faecalis} are very promising. Although 2 patients had infection relapse, the protocol had been violated in 1 patient and the other patient may have had concomitant aortic graft infection, possibly requiring

### Table 2. Outcomes*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLAR \textit{E. faecalis} Endocarditis</th>
<th>Non-HLAR \textit{E. faecalis} Endocarditis</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥42 d, n (%)</td>
<td>13 (61.9)</td>
<td>14 (63.6)</td>
<td>27 (62.8)</td>
</tr>
<tr>
<td>Mean, d</td>
<td>35.5</td>
<td>34</td>
<td>34.7</td>
</tr>
<tr>
<td>Median (range), d</td>
<td>42 (9–45)</td>
<td>42 (5–48)</td>
<td>42 (5–48)</td>
</tr>
<tr>
<td><strong>Adverse events, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20 (95.2)</td>
<td>21 (95.4)</td>
<td>41 (95.3)</td>
</tr>
<tr>
<td>Rash and fever</td>
<td>0</td>
<td>1 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (4.8)</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td><strong>Complications, n (%)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (42.9)</td>
<td>16 (72.7)</td>
<td>25 (58.1)</td>
</tr>
<tr>
<td>Cerebral embolism</td>
<td>5 (23.8)</td>
<td>6 (27.3)</td>
<td>11 (25.6)</td>
</tr>
<tr>
<td>Paravalvular abscess</td>
<td>1 (4.8)</td>
<td>2 (9.1)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>2 (9.1)</td>
<td>2 (4.6)</td>
</tr>
<tr>
<td>Mesenteric embolism</td>
<td>1 (4.8)</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Embolic myocardial infarction</td>
<td>1 (4.8)</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Perivalvular leak</td>
<td>0</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td><strong>Surgery, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve replacement</td>
<td>3 (14.3)</td>
<td>4 (18.2)</td>
<td>7 (16.3)</td>
</tr>
<tr>
<td>Abscess</td>
<td>1 (4.8)</td>
<td>3 (13.6)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Mycotic aortic aneurysm</td>
<td>1 (4.8)</td>
<td>1 (4.6)</td>
<td>2 (4.6)</td>
</tr>
<tr>
<td><strong>Failures, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death during treatment</td>
<td>6 (28.6)</td>
<td>8 (36.4)</td>
<td>14 (32.6)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (28.6)</td>
<td>4 (18.2)</td>
<td>10 (23.3)</td>
</tr>
<tr>
<td>Embolic events</td>
<td>4 (19)</td>
<td>2 (9.1)</td>
<td>6 (13.9)</td>
</tr>
<tr>
<td>Cerebral</td>
<td>0</td>
<td>1 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>1 (4.8)</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Myocardial</td>
<td>1 (4.8)</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Death during follow-up</td>
<td>0</td>
<td>2 (9.1)</td>
<td>2 (4.6)</td>
</tr>
<tr>
<td>Cerebral embolism†</td>
<td>0</td>
<td>1 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>1 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Relapses</td>
<td>0</td>
<td>2 (9.1)</td>
<td>2 (4.6)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>0</td>
<td>1 (4.6)</td>
<td>1 (2.3)</td>
</tr>
</tbody>
</table>

* \(P\) values were nonsignificant for all comparisons (\(P > 0.05\), unless otherwise indicated. \textit{E. faecalis} = \textit{Enterococcus faecalis}; HLAR = high-level aminoglycoside resistance.

† \(P = 0.021\).

‡ The patient who died of cerebral embolism was 1 of those who had relapse. It counts as only 1 failure event for the total.
Ampicillin plus Ceftriaxone for *Enterococcus faecalis* Endocarditis

**Figure. Kaplan–Meier curve of time to failure for any reason.**

![Kaplan–Meier curve](image)

HLAR = high-level aminoglycoside resistance.

surgery or lifelong antibiotic treatment. The incidence of relapse in our series (2 of 43 [4.6%] patients) was similar to that reported in 2 recent studies: 3 of 93 (3%) patients in Olaison and Schadewitz’s study (21) and 3.9% in Almirante and colleagues’ study (8).

With regard to adverse effects, the treatment was tolerated well. Only 2 patients had treatment-related side effects, and therapy had to be suspended in only 1 patient owing to fever and skin rash. No cases of nephrotoxicity occurred.

The limitations of our study are the small size of the sample and lack of a randomly assigned comparison group.

In conclusion, a double *β*-lactam combination (ampicillin plus ceftriaxone) may be the choice of therapy for patients with endocarditis due to HLAR *E. faecalis* and may be a reasonable alternative for patients with non-HLAR *E. faecalis* endocarditis, but it is associated with an increased risk for nephrotoxicity.

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