Annals of Internal Medicine | ARTICLE

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

Joan Gavaldà, MD; Oscar Len, MD; José M. Miró, MD; Patricia Muñoz, MD; Miguel Montejo, MD; Aristides Alarcón, MD; Julián de la Torre-Cisneros, MD; Carmen Peña, MD; Xavier Martínez-Lacasa, MD; Cristina Sarria, MD; Germán Bou, MD; José M. Aguado, MD; Enrique Navas, MD; Joan Romeu, MD; Francesc Marco, MD; Carmen Torres, MD; Pilar Tornos, MD; Ana Planes, MD; Vicenç Falcó, MD; Benito Almirante, MD; and Albert Pahissa, MD

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.

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 Treatment was withdrawn in 1 case because of fever and skin rash.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.

Ann Intern Med. 2007;146:574-579. www.annals.org
For author affiliations, see end of text.

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 (11). 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

See also:

Print
Editors' Notes 575
Summary for Patients I-56

Web-Only
Conversion of figure and tables into slides

30 to 60 minutes, with ceftriaxone given just after the ampicillin infusion. In patients at risk for biliary toxicity due to ceftriaxone (2 cases), cefotaxime 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.

Context

The American Heart Association recommends a 4- to 6-week course of penicillin or ampicillin plus an aminoglycoside for treating enterococcal endocarditis. Infection with *Enterococcus faecalis* organisms that have high-level aminoglycoside resistance (HLAR) renders this regimen ineffective.

Contribution

This observational, open-label, nonrandomized trial found that a 6-week course of intravenous ampicillin plus ceftriaxone effectively treated patients who had endocarditis due to HLAR *E. faecalis* or non-HLAR *E. faecalis* and could not tolerate aminoglycosides because of nephrotoxicity.

Caution

Effectiveness of the regimen depended on the participants' ability to complete the treatment protocol.

Implication

A combination of ampicillin and ceftriaxone may be effective treatment for previously untreatable HLAR enterococcal endocarditis.

—The Editors

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

Table 1. **Demographic and Clinical Features in 43 Episodes of Enterococcal Endocarditis***

Variable	HLAR *E. faecalis* Endocarditis	Non-HLAR *E. faecalis* Endocarditis	Overall
Patients, *n (%)*	21 (48.8)	22 (51.2)	43 (100)
Age			
Mean, *y*	61.3	64.8	63
Median (range)	65 y (6 mo–82 y)	68 y (24–86 y)	66.5 y (6 mo–86 y)
Sex, *n (%)*			
Male	15 (71.4)	13 (59.1)	28 (65.1)
Female	6 (28.6)	9 (40.9)	15 (34.9)
Underlying diseases or event, *n (%)*			
Diabetes mellitus	4 (19)	5 (22.7)	9 (20.9)
Chronic renal failure	3 (14.3)	5 (22.7)	8 (18.6)
Cirrhosis	1 (4.8)	0	1 (2.3)
Alcoholism	1 (4.8)	1 (4.5)	2 (4.6)
HIV	1 (4.8)	1 (4.5)	2 (4.6)
Renal transplantation	1 (4.8)	1 (4.5)	2 (4.6)
Heart transplantation	1 (4.8)	0	1 (2.3)
Neoplasm	1 (4.8)	1 (4.5)	2 (4.6)
Source of infection, *n (%)*†			
Community-acquired infection	13 (61.9)	20 (90.9)	33 (76.7)
Health care–associated infection	8 (38.1)	2 (9.1)	10 (23.3)
Predisposing factors, *n (%)*			
None identified	8 (38.1)	6 (27.3)	14 (32.6)
Identified	13 (61.9)	16 (72.7)	29 (67.4)
Heart valve disease	2 (9.5)	2 (9.1)	4 (9.3)
Prosthetic valve	8 (38.1)	10 (45.5)	18 (41.9)
Cardiomyopathy	1 (4.8)	2 (9.1)	3 (7)
Injection drug abuse	0	1 (4.6)	1 (2.3)
Urologic procedure	4 (19)	1 (4.6)	5 (11.6)
Gastrointestinal procedure	1 (4.8)	0	1 (2.3)
Location, *n (%)*			
Aortic valve	11 (52.4)	14 (63.6)	25 (58.1)
Mitral valve	6 (28.6)	5 (22.7)	11 (25.6)
Aortic and mitral valve	3 (14.3)	1 (4.6)	4 (9.3)
Tricuspid valve	0	1 (4.6)	1 (2.3)
Pulmonary valve	0	1 (4.6)	1 (2.3)
Tricuspid and aortic valve	1 (4.8)	0	1 (2.3)
Duration of symptoms, *d*			
Mean	30.7	28.9	29.8
Median (range)	17 (2–150)	20.5 (1–120)	20 (1–150)

* *P* values were nonsignificant for all comparisons ($P > 0.05$), unless otherwise indicated. *E. faecalis* = *Enterococcus faecalis*; HLAR = high-level aminoglycoside resistance.
† $P = 0.024$.

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 enterococcal endocarditis caused by strains resistant to penicillin, aminoglycosides, and vancomycin (on the basis of our preliminary report in 20 patients [13 with HLAR enterococcal 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 *E. faecalis* and the experience with linezolid is scarce and controversial in patients with *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 *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 *E. faecalis*.

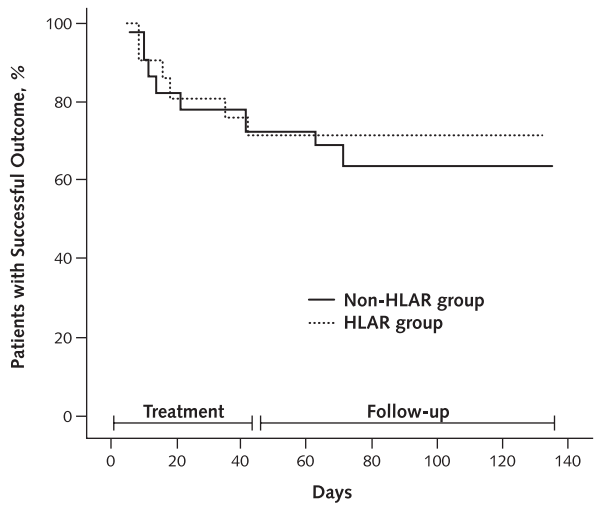
Toxicity resulting from aminoglycosides depends mainly on the duration of treatment, the age of the patient, and the total amount of aminoglycoside administered. Because enterococcal endocarditis generally occurs in older individuals, older patients would benefit from less-toxic therapy. The results obtained in our small cohort of patients with non-HLAR *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***

Variable	HLAR *E. faecalis* Endocarditis	Non-HLAR *E. faecalis* Endocarditis	Overall
Duration of treatment			
≥42 d, *n (%)*	13 (61.9)	14 (63.6)	27 (62.8)
Mean, *d*	35.5	34	34.7
Median (range), *d*	42 (9–45)	42 (5–48)	42 (5–48)
Adverse events, *n (%)*			
None	20 (95.2)	21 (95.4)	41 (95.3)
Rash and fever	0	1 (4.6)	1 (2.3)
Leukopenia	1 (4.8)	0	1 (2.3)
Complications, *n (%)*†	9 (42.9)	16 (72.7)	25 (58.1)
Heart failure	5 (23.8)	6 (27.3)	11 (25.6)
Cerebral embolism	1 (4.8)	5 (22.7)	6 (13.9)
Paravalvular abscess	1 (4.8)	2 (9.1)	3 (7)
Arrhythmia	0	2 (9.1)	2 (4.6)
Mesenteric embolism	1 (4.8)	0	1 (2.3)
Embolic myocardial infarction	1 (4.8)	0	1 (2.3)
Perivalvular leak	0	1 (4.6)	1 (2.3)
Surgery, *n (%)*	3 (14.3)	4 (18.2)	7 (16.3)
Valve replacement	1 (4.8)	3 (13.6)	4 (9.3)
Abscess	1 (4.8)	1 (4.6)	2 (4.6)
Mycotic aortic aneurysm	1 (4.8)	0	1 (2.3)
Failures, *n (%)*	6 (28.6)	8 (36.4)	14 (32.6)
Death during treatment	6 (28.6)	4 (18.2)	10 (23.3)
Heart failure	4 (19)	2 (9.1)	6 (13.9)
Embolic events			
Cerebral	0	1 (4.6)	1 (2.3)
Mesenteric	1 (4.8)	0	1 (2.3)
Myocardial	1 (4.8)	0	1 (2.3)
Pulmonary	0	1 (4.6)	1 (2.3)
Death during follow-up	0	2 (9.1)	2 (4.6)
Cerebral embolism‡	0	1 (4.6)	1 (2.3)
Heart failure	0	1 (4.6)	1 (2.3)
Relapses	0	2 (9.1)	2 (4.6)
Adverse events	0	1 (4.6)	1 (2.3)

* *P* values were nonsignificant for all comparisons ($P > 0.05$), unless otherwise indicated. *E. faecalis* = *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.

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



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 treatment of choice 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.

From the Hospital Universitari Vall d'Hebron, Institut d'Investigacions Biomediques August Pi i Sunyer, Hospital de Bellvitge, Mutua de Terrassa, and Hospital Germans Tries i Pujol, Barcelona, Spain; Hospital Gregorio Marañón, Hospital Universitario de La Princesa, Hospital Doce de Octubre, and Hospital Ramón y Cajal, Madrid, Spain; Hospital de Cruces, Barakaldo, Spain; Hospital Virgen del Rocío, Seville, Spain; Hospital Reina Sofía, Córdoba, Spain; Hospital Juan Canalejo, La Coruña, Spain; and Universidad de La Rioja, Logroño, Spain.

Note: Presented in part at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, 16–19 December 2001 (abstract 1342).

Acknowledgment: The authors thank Celine Cavallo for English-language assistance.

Grant Support: Dr. Len received a research grant from Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008), and Dr. Miró received a research grant from Institut d'Investigacions Biomediques August Pi i Sunyer.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Joan Gavaldà, MD, Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain; e-mail, jgavalda@ir.vhebron.net.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, et al.** Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. 2005;111:e394-434. [PMID: 15956145]

2. **Spiegel CA, Huycke M.** Endocarditis due to streptomycin-susceptible *Enterococcus faecalis* with high-level gentamicin resistance. Arch Intern Med. 1989;149:1873-5. [PMID: 2504123]

3. **Turano A, Ravizzola G, Peroni L, Ceruti T, Greco LM, Pitzus E, et al.** A multicentre study: *Staphylococcus* and *Enterococcus* susceptibility to antibiotics. Eur J Epidemiol. 1994;10:567-72. [PMID: 7859856]

4. **Smyth EG, Stevens PJ, Holliman RE.** Prevalence and susceptibility of highly gentamicin resistant *Enterococcus faecalis* in a south London teaching hospital. J Antimicrob Chemother. 1989;23:633-9. [PMID: 2501271]

5. **Moellering RC Jr, Wennersten C, Medrek T, Weinberg AN.** Prevalence of high-level resistance to aminoglycosides in clinical isolates of enterococci. Antimicrobial Agents Chemother (Bethesda). 1970;10:335-40. [PMID: 5521352]

6. **Jones RN, Sader HS, Erwin ME, Anderson SC.** Emerging multiply resistant enterococci among clinical isolates. I. Prevalence data from 97 medical center surveillance study in the United States. Enterococcus Study Group. Diagn Microbiol Infect Dis. 1995;21:85-93. [PMID: 7628198]

7. **Gordon S, Swenson J, Facklam R, Pigott N, Hill B, Cooksey R, et al.** A multicenter study of the epidemiology of enterococcal infections [Abstract]. In: Program and Abstracts of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, Texas, 17-20 September 1989. Washington, DC: American Soc for Microbiology; 1989:abstract 233.

8. **Almirante B, Peña C, Miró JM, Gurguí M, Aguado JM, Alarcón A, et al.** Enterococcal endocarditis a cooperative study of 178 cases [Abstract]. In: Program and Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, 24-27 September 1998. Washington, DC: American Soc for Microbiology; 1998:abstract 551.

9. **Cirak MY, Sultan N.** Prevalence of high level aminoglycoside and vancomycin resistance among enterococci in Turkey. Acta Microbiol Pol. 1998;47:267-73. [PMID: 9990710]

10. **Calderwood SA, Wennersten C, Moellering RC Jr, Kunz LJ, Krogstad DJ.** Resistance to six aminoglycosidic aminocyclitol antibiotics among enterococci: prevalence, evolution, and relationship to synergism with penicillin. Antimicrob Agents Chemother. 1977;12:401-5. [PMID: 242911]

11. **Gavaldà J, Torres C, Tenorio C, López P, Zaragoza M, Capdevila JA, et al.** Efficacy of ampicillin plus ceftriaxone in treatment of experimental endocarditis due to *Enterococcus faecalis* strains highly resistant to aminoglycosides. Antimicrob Agents Chemother. 1999;43:639-46. [PMID: 10049280]

12. **Gavaldá J, Onrubia PL, Gómez MT, Gomis X, Ramírez JL, Len O, et al.** Efficacy of ampicillin combined with ceftriaxone and gentamicin in the treatment of experimental endocarditis due to *Enterococcus faecalis* with no high-level resistance to aminoglycosides. J Antimicrob Chemother. 2003;52:514-7. [PMID: 12917251]

13. **Durack DT, Lukes AS, Bright DK.** New criteria for diagnosis of infective

endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96:200-9. [PMID: 8154507]

14. **Gavaldà J, Miró J, Torres C, de La Torre-Cisneros J, Muñoz P, Peña C, et al.** Efficacy of ampicillin plus ceftriaxone or cefotaxime in treatment of endocarditis due to *Enterococcus faecalis* [Abstract]. In: Programs and Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, 16-19 December 2001. Washington, DC: American Soc for Microbiology; 2001:abstract 1342.

15. **Facklam RR, Collins MD.** Identification of *Enterococcus* species isolated from human infections by a conventional test scheme. J Clin Microbiol. 1989;27:731-4. [PMID: 2656745]

16. **Sahm DF, Torres C.** Effects of medium and inoculum variations on screening for high-level aminoglycoside resistance in *Enterococcus faecalis*. J Clin Microbiol. 1988;26:250-6. [PMID: 3125217]

17. **Lewis PJ, Martino P, Mosconi G, Harding I.** Teicoplanin in endocarditis: a multicentre, open European study. Chemotherapy. 1995;41:399-411. [PMID: 8521743]

18. **Zimmer SM, Caliendo AM, Thigpen MC, Somani J.** Failure of linezolid treatment for enterococcal endocarditis. Clin Infect Dis. 2003;37:e29-30. [PMID: 12884185]

19. **Olesen HV, Møller JK.** [Enterococcal infections. Clinical findings and treatment considering antibiotic resistance in Denmark]. Ugeskr Laeger. 2002;164:2386-90. [PMID: 12024841]

20. **Selton-Suty C, Hoen B, Grentzinger A, Houplon P, Maignan M, Juillière Y, et al.** Clinical and bacteriological characteristics of infective endocarditis in the elderly. Heart. 1997;77:260-3. [PMID: 9093046]

21. **Olaison L, Schadewitz K.** Enterococcal endocarditis in Sweden, 1995-1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis. 2002;34:159-66. [PMID: 11740702]

22. **Hricak V Jr, Kovacik J, Marx P, Fischer V, Krcmery V Jr.** Endocarditis due to *Enterococcus faecalis*: risk factors and outcome in twenty-one cases from a five year national survey [Letter]. Scand J Infect Dis. 1998;30:540-1. [PMID: 10066066]

Current Author Addresses: Drs. Gavaldà, Len, Tornos, Planes, Falcó, Almirante, and Pahissa: Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain.
Drs. Miró and Marco: Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer, Calle Villarroel, 170, 08036 Barcelona, Spain.
Dr. Muñoz: Hospital Gregorio Marañón, Calle Doctor Esquerdo, 46, 28007 Madrid, Spain.
Dr. Montejo: Hospital de Cruces, Plaza de Cruces, s/n, 48903 Cruces/Barakaldo, Spain.
Dr. Alarcón: Hospital Virgen del Rocío, Avenida Manuel Siurot, s/n, 41013 Sevilla, Spain.
Dr. de la Torre-Cisneros: Hospital Reina Sofía, Menéndez Pidal, s/n, 14004 Córdoba, Spain.
Dr. Peña: Hospital de Bellvitge, Feixa Llarga, s/n, 08907 Hospitalet de Llobregat, Barcelona, Spain.
Dr. Martínez-Lacasa: Hospital Mutua de Terrassa, Plaça Dr. Robert, 5, 08221 Terrassa, Barcelona, Spain.
Dr. Sarria: Hospital Universitario de La Princesa, Diego de León, 62, 28006 Madrid, Spain.
Dr. Bou: Hospital Juan Canalejo, Lugar Jubias de Arriba, La Coruña, Spain.
Dr. Aguado: Hospital Doce de Octubre, Avenida de Córdoba, s/n, 28041 Madrid, Spain.
Dr. Navas: Hospital Ramón y Cajal, Carretera de Colmenar Viejo, Km 9, 1, 28034 Madrid, Spain.
Dr. Romeu: Hospital Germans Tries i Pujol, Carretera de Canyet s/n, 08916 Badalona, Barcelona, Spain.
Dr. Torres: Universidad de La Rioja, Avenida de La Paz, 93, 26006 Logroño, Spain.

Author Contributions: Conception and design: J. Gavaldà, O. Len.
Analysis and interpretation of the data: J. Gavaldà, O. Len.
Drafting of the article: J. Gavaldà, O. Len.
Critical revision of the article for important intellectual content: J. Gavaldà, O. Len, V. Falcó, B. Almirante, A. Pahissa.
Final approval of the article: J. Gavaldà, O. Len, J.M. Miró, P. Muñoz, M. Montejo, A. Alarcón, J. de la Torre-Cisneros, C. Peña, X. Martínez-Lacasa, C. Sarria, G. Bou, J.M. Aguado, E. Navas, J. Romeu, F. Marco, C. Torres, P. Tornos, A. Planes, V. Falcó, B. Almirante, A. Pahissa.
Provision of study materials or patients: J. Gavaldà, O. Len, J.M. Miró, P. Muñoz, M. Montejo, A. Alarcón, J. de la Torre-Cisneros, C. Peña, X. Martínez-Lacasa, C. Sarria, G. Bou, J.M. Aguado, E. Navas, J. Romeu, F. Marco, C. Torres, P. Tornos, A. Planes, V. Falcó, B. Almirante.
Collection and assembly of data: J. Gavaldà, O. Len.