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REPLY

Reply to Cuervo et al. And Horinouchi et al.

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Dear Editor,

We thank Cuervo et al., and Horinouchi et al. for their interesting comments on our study.

Cuervo et al. highlighted the high frequency of relapse observed in our study. If we exclude patients who were not treated with conventional treatment (aminopenicillin plus either gentamicin [A-G] or ceftriaxone [A-C]), the relapse rate at 6 months was 7.7% (20/260). This rate remains higher than the 3.4% observed at 6-months in the Pericàs et al. study but closer to the 7%-10% observed in recent studies [1–4]. Several factors could contribute to this high relapse rate:

1. The rate of surgery during treatment observed in our study (32%) was lower than that reported in other studies (40-42%) [1,4]. Indeed, this variable has been identified in our study as a protective factor for relapse, which is confirmed by Cuervo et al. A higher relapse rate is found in studies with lower surgery rates (12-19%) [2,3]. The relatively low rate of surgery in our study is partially explained by the inclusion of 35% of patients initially managed in hospitals without on-site heart surgery: 18% (17/97) of them underwent surgery during treatment.

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2. As suggested by Horinouchi et al., the prolonged and systematic clinical and biological surveillance performed in some of the centers participating to the EFEMER study may have contributed to the high relapse rate. Unfortunately, the follow-up of patients was not standardized. In fact, there is no official guideline on biological follow-up for relapse screening in asymptomatic patients [5,6]. We hope that our results will promote a more careful surveillance of patients that have been treated for *E. faecalis* endocarditis, especially without surgery.
3. Cuervo et al. suggest that the high risk of relapse observed in our study could arise from an incorrect use of gentamicin in cases due to isolates with High-Level Aminoglycoside Resistance (HLAR). Over the five-year study period (2015 to 2019), in France, the rate of HLAR among *E. faecalis* invasive isolates is estimated around 12% [7]. In our study, this information was available for 183 of the 279 patients. Only 9 (5%) isolates exhibited HLAR. Of the 11 relapsed patients initially treated with A-G or A-G/A-C, only one was infected by an HLAR isolate. This patient had received 2 days of A-G followed by 40 days of A-C. Based on this evidence, we do not believe that the gentamicin resistance profile had an impact on the relapse rate.

Cuervo et al. make remarkable observations on the protective role of surgery during treatment against relapse. In our cohort, this protective role was still found in multivariate analysis when considering only the 260 patients who received conventional treatment (aSHR 0.08, CI 95% 0.01-0.57; P=.01). The only relapsed patient operated during treatment had a bioprosthetic aortic valve replacement after 7 days of A-G and received after surgery 35 days of amoxicillin alone. We agree that the risk of relapse should be considered in the decision for surgery. But cardiac surgery is not always possible in patients with EFIE, who are older and have more comorbidities than patients with endocarditis due to other bacteria [1].

We had voluntarily not assessed the risk factors for relapse because of the small number of events and to avoid alpha-risk inflation. However, at the request of Cuervo et al. we present this univariate analysis based on the Fine and Gray model in Table 1. The presence of an embolic event was associated with the risk of relapse; this was confirmed in the multivariate model (aSHR 3.74, CI 95% 1.32-10.58; P=.01). In the study by Pericàs et al., the only risk factor for relapse was the persistence of bacteremia more than 7 days after the start of effective antibiotic therapy [1]. Surprisingly in our analysis, persistent bacteremia more than 3 days after starting antibiotics seemed to be protective against relapse risk. However, of the 14 patients in question, 8 died within the year. In multivariate analysis, this criterion was associated with death (aHR 3.01, CI 95% 1.41-6.50; P=.005).

Finally, we agree with Horinouchi et al. that the practices of each center may influence the prognosis of patients. Unfortunately, the low number of patients in some centers did not allow us to perform an analysis to control for this center effect. In addition, some patients were transferred

from one center to another, which would have biased this analysis. Instead, we present in Table 2 a description of the main patients' characteristics, management, and outcome according to the initial care center.

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References

1. Pericàs JM, Llopis J, Muñoz P, et al. A Contemporary Picture of Enterococcal Endocarditis. *J Am Coll Cardiol* **2020**; 75:482–494.
2. Dahl A, Iversen K, Tonder N, et al. Prevalence of Infective Endocarditis in *Enterococcus faecalis* Bacteremia. *J Am Coll Cardiol* **2019**; 74:193–201.
3. Briggs S, Broom M, Duffy E, et al. Outpatient continuous-infusion benzylpenicillin combined with either gentamicin or ceftriaxone for enterococcal endocarditis. *J Antimicrob Chemother* **2021**;
4. Herrera-Hidalgo L, Lomas-Cabezas JM, López-Cortés LE, et al. Ampicillin Plus Ceftriaxone Combined Therapy for *Enterococcus faecalis* Infective Endocarditis in OPAT. *J Clin Med* **2021**; 11:7.
5. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditisThe Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* **2015**; 36:3075–3128.
6. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation* **2015**; 132:1435–1486.
7. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report for 2019. Stockholm: ECDC. **2020**;

Table 1. Univariate analysis, in Fine-Gray model, of risk factors for one-year relapse in endocarditis due to *E. faecalis* treated with aminopenicillin plus either gentamicin or ceftriaxone combinations in overall cohort (n=260) and for patients non-operated during treatment (n=170).

Variable	All patients (n=260)		Patients not operated during treatment (n=170)	
	Hazard Ratio (CI 95%)	P Value	Hazard Ratio (CI 95%)	P Value
Demographic features				
Gender, male	0.95 (0.35-2.57)	.91	0.95 (0.35-2.50)	.93
Initial admission in hospital with cardiac surgery department	1.26 (0.52-3.06)	.61	1.61 (0.66-3.94)	.29
Comorbidities				
Age	1.03 (0.99-1.06)	.18	1.00 (0.97-1.04)	.86
Diabetes mellitus	0.42 (0.12-1.39)	.15	0.46 (0.14-1.52)	.20
Congestive heart failure	0.99 (0.42-2.33)	.99	0.76 (0.32-1.79)	.53
Moderate/severe chronic renal failure	0.22 (0.03-1.60)	.13	0.22 (0.03-1.65)	.14
Neoplasm	0.98 (0.33-2.89)	.97	0.99 (0.33-2.95)	.99
Charlson comorbidity index	0.99 (0.89-1.11)	.89	0.94 (0.83-1.06)	.29
Type of IE and underlying cardiac condition				
Native valve IE	0.69 (0.30-1.56)	.37	0.96 (0.42-2.23)	.93
Prosthetic valve IE	1.45 (0.64-3.29)	.37	1.04 (0.45-2.40)	.93
TAVI	1.12 (0.34-3.73)	.85	0.75 (0.22-2.49)	.63
Intra-Cardiac Device	1.08 (0.40-2.80)	.87	0.87 (0.32-2.32)	.77
Previous endocarditis	0.93 (0.22-3.91)	.93	0.77 (0.18-3.22)	.72
Community endocarditis	1.00 (0.41-2.43)	.99	1.00 (0.45-2.68)	.84
Persistent bacteremia \geq 3 days	0.00 (0.00-0.00)	<.0001	0.00 (0.00-0.00)	<.0001
Echocardiography findings				
Vegetation	0.74 (0.29-1.87)	.52	1.02 (0.40-2.58)	.97
Echocardiographic complication	0.66 (0.29-1.49)	.32	0.96 (0.42-2.20)	.92
Clinical complication				
Acute heart failure	1.40 (0.48-4.10)	.54	2.64 (0.78-8.80)	.12
Acute kidney injury	1.05 (0.46-2.30)	.91	1.48 (0.64-3.42)	.36
Systemic embolic event	3.03 (1.19-7.60)	.02	4.20 (1.58-11.68)	.004
CNS embolism	2.22 (0.96-5.13)	.06	2.78 (1.19-6.40)	.02
Vertebral osteomyelitis	2.85 (1.13-7.16)	.03	2.89 (1.15-7.26)	.02
Valve surgery				
Indicated	0.58 (0.25-1.32)	.19	1.40 (0.63-3.54)	.36
Indicated but not performed	1.66 (0.61-4.51)	.32	1.03 (0.38-2.82)	.95
Performed during antibiotic treatment	0.08 (0.01-0.63)	.02	-	-

Table 2. Characteristics, management, and outcome of 279 cases of endocarditis due to *E. faecalis* according to the initial care center.

Variable	Center#1* (n=40)	Center#2* (n=39)	Center#3* (n=37)	Center#4* (n=36)	Center#5* (n=22)	Center#6 (n=20)	Center#7 (n=17)	Center#8 (n=16)	Center#9* (n=14)	Center#10 (n=14)	Center#11 (n=8)	Center#12 (n=6)	Center#13 (n=5)	Center#14* (n=5)
Demographic and clinical features														
Age, years	74 [69-82]	71 [60-82]	72 [65-78]	70 [65-82]	72 [66-84]	81 [74-84]	74 [59-82]	76 [66-86]	70 [65-79]	83 [76-89]	81 [55-86]	82 [58-85]	80 [79-80]	78 [74-82]
Gender, male	34 (85.0)	30 (76.9)	30 (81.1)	28 (77.8)	17 (77.3)	15 (75.0)	15 (88.2)	12 (75.0)	11 (78.6)	9 (64.3)	7 (87.5)	5 (83.3)	3 (60.0)	5 (100.0)
Congestive heart failure	10 (25.0)	13 (33.3)	14 (37.8)	13 (36.1)	11 (50.0)	10 (50.0)	2 (11.8)	7 (43.8)	2 (14.3)	6 (42.9)	4 (50.0)	1 (16.7)	2 (40.0)	2 (40.0)
Charlson comorbidity index	5 [4-6]	4 [2-7]	5 [3-7]	6 [3-7]	5 [3-8]	6 [4-8]	2 [1-6]	5 [4-6]	5 [3-7]	6 [5-8]	5 [2-8]	5 [4-9]	6 [6-8]	7 [6-9]
Prosthetic valve IE	16 (40.0)	16 (41.0)	16 (43.2)	15 (41.7)	9 (40.9)	8 (40.0)	7 (41.2)	7 (43.8)	4 (28.6)	6 (42.9)	4 (50.0)	3 (50.0)	3 (60.0)	3 (60.0)
Acute heart failure	9 (22.5)	18 (46.2)	16 (43.2)	18 (50.0)	13 (59.1)	11 (55.0)	4 (23.5)	6 (37.5)	4 (28.6)	9 (64.3)	4 (50.0)	1 (16.7)	1 (20.0)	2 (40.0)
Management														
Valve surgery indicated	23 (57.5)	28 (71.8)	24 (64.9)	17 (47.2)	14 (63.6)	9 (45.0)	3 (17.6)	2 (12.5)	5 (35.7)	8 (57.1)	3 (37.5)	2 (33.3)	2 (40.0)	2 (40.0)
Valve surgery performed during antibiotic treatment	19 (47.5)	20 (51.3)	15 (40.5)	12 (33.3)	10 (45.5)	5 (25.0)	2 (11.8)	0 (0.0)	4 (28.6)	0 (0.0)	1 (12.5)	1 (16.7)	0 (0.0)	1 (20.0)
Total duration of antibiotic, days	42 [42-43]	43 [41-53]	42 [31-43]	42 [41-45]	42 [26-43]	42 [42-45]	43 [38-46]	41 [38-43]	42 [36-45]	42 [23-45]	42 [41-46]	42 [41-43]	42 [29-42]	42 [21-42]
Amoxicillin monotherapy	1 (2.5)	1 (2.6)	0 (0.0)	3 (8.3)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (16.7)	1 (20.0)	0 (0.0)
A-C combination	12 (30.0)	26 (66.7)	5 (13.5)	17 (47.2)	14 (63.6)	4 (20.0)	4 (23.5)	8 (50.0)	5 (35.7)	8 (57.1)	6 (75.0)	4 (66.7)	0 (0.0)	1 (20.0)
A-G combination	10 (25.0)	1 (2.6)	23 (62.2)	8 (22.2)	1 (4.5)	8 (40.0)	10 (58.8)	5 (31.3)	8 (57.1)	2 (14.3)	1 (12.5)	1 (16.7)	4 (80.0)	1 (20.0)
A-G/A-C combinations	16 (40.0)	11 (28.2)	9 (24.3)	6 (16.7)	5 (22.7)	5 (25.0)	3 (17.6)	3 (18.8)	0 (0.0)	2 (14.3)	1 (12.5)	0 (0.0)	0 (0.0)	2 (40.0)
Other treatment	1 (2.5)	0 (0.0)	0 (0.0)	2 (5.6)	2 (9.1)	2 (10.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
One-year outcome														
Relapse	6 (15.0)	2 (5.1)	3 (8.1)	6 (16.7)	0 (0.0)	1 (5.0)	0 (0.0)	1 (6.3)	1 (7.1)	2 (14.3)	2 (25.0)	1 (16.7)	1 (20.0)	0 (0.0)
Death	8 (20.0)	7 (17.9)	4 (10.8)	10 (27.8)	10 (45.5)	6 (30.0)	5 (29.4)	4 (25.0)	3 (21.4)	8 (57.1)	3 (37.5)	1 (16.7)	2 (40.0)	3 (60.0)

Quantitative variables are expressed as median [IQR], qualitative variables are expressed by numbers (%).

* Center with on-site cardiac surgery ward