CORRESPONDENCE

Therapeutic issues in relapsing *Enterococcus faecalis* endocarditis

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Dear Editor,

We have read with great interest the article by Daneels et al. [1] which analyzes the treatment approach and risk of relapse in a large cohort of patients with definite *Enterococcus faecalis* endocarditis (EFIE). Although relatively less serious than endocarditis caused by other microorganisms, EFIE is fearsome due to the high risk of relapse [2]. We want to congratulate the authors for conducting an ambitious study that encompasses 14 French hospitals and elapses 4 years, which was very much needed in an elusive yet increasingly important infection as EFIE. Yet, there are several aspects tackled in Daneels and colleagues' work that deserve particular attention, and we would like to address these:

1. We share authors' view that aminopenicillin monotherapy is an inadequate treatment for EFIE. Consequently, the group treated with aminopenicillin therapy should have been excluded from the analysis. The number of relapses due to monotherapy failure likely contributed to an overall increased count of relapses in a cohort otherwise receiving treatments that are recommended by current guidelines.
2. The rates of *E. faecalis* isolates with high-level aminoglycoside resistance (roughly 40% in Europe) [3] should have been provided as some relapses might have been due to the incorrect use of gentamicin to treat EFIE caused by such strains, which passed unnoticed to treating physicians.
3. The authors argue that the overall high relapse rate (9.3% at one-year) should be nuanced by the long follow-up period and the demographics of patients managed in peripheral hospitals. However, this relapse rate still seems unusually high

compared to the percentages described in other large European and International cohorts [4-7] (see **Table 1**) which were of 6% at one year in the Danish cohort and 3.4% and 1.5% at six months in the Spanish and international collaboration on endocarditis (ICE) cohorts, respectively.

4. A multivariate analysis of risk factors for relapse is missing and it would be very informative to perform it in the overall cohort and in patients who did not undergo surgery. Cases treated with an aminopenicillin monotherapy should be excluded from this analysis for the reasons stated above. It is very likely that surgery will be a protective variable in the global analysis. For this reason, it is very important to perform the analysis in non-operated patients, to determine which clinical or therapeutic variables were associated with relapse.
5. In our opinion, the finding from Daneels and colleagues' work that bears a greater potential to influence clinical practice is not related to antibiotic treatment but rather to cardiac surgery. Notably, there were virtually no documented relapses amongst patients undergoing valve surgery (the only relapse occurred in a patient treated with aminopenicillin monotherapy). In addition, in the Spanish and in the ICE cohorts, cardiac surgery reduced the risk of relapse by 66% and 73%, respectively, compared to non-operated patients (see **Table 1**). Taken together, the cardiac surgery indication for EFIE might be reassessed, beyond the classic indications for surgery stated in the guidelines [8,9].

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Table. Comparison of relapse rates between different national and international multicentric cohorts

Cohort	Antibiotic treatment	Overall relapse rate N/total (%; 95% CI)	Relapse/NO surgery N/total (%; 95% CI)	Relapse/Surgery performed N/total (%; 95% CI)	*P* value
French cohort [1]	**A+G**	9/83 (10.84%; 4.15-17.53)*	20/172 (11.63%; 6.84-16.42)	0/98 (0.00%; 0.00-0.04)	0.001
	A+C	10/114 (8.77%; 3.58-13.96)*			
	A+G → A+C	1/63 (1.59%; 0.00-4.67)*			
Danish cohort [4]	**A+G$^{\beta}$**	5/84 (5.95%; 0.89-11.01)**	4/55 (7.27%; 0.41-14.14)	1/29 (3.45%; 0.00-10.09)	0.481
Spanish cohort [5]	**A+G or A+C**	16/468 (3.42%; 1.77-5.07)*	13/276 (4.71%; 2.21-7.21)	3/192 (1.56%; 0.00-3.32)	0.066
ICE Cohort* **	**A+G or A+C**	13/852 (1.52%; 0.70-2.35)*	11/512 (2.15%; 0.89-3.40)	2/340 (0.59%; 0.00-1.40)	0.069

A: Amoxicillin/Ampicillin. **G:** Gentamicin. **C:** Ceftriaxone. **β:** Two different gentamicin regimens.
*6-months relapse. **1-year relapse. *** Unpublished data.