Reply to Gelfand et al and Solla

To the Editor—We appreciate the interest Gelfand et al [1] have shown regarding our observational, nonrandomized, comparative multicenter study [2]. Infective endocarditis (IE) is an uncommon, severe disease [3], and it is inevitable that randomized trials on this condition are lacking. In our observational study, the combination of ampicillin and ceftriaxone (AC) was compared with the standard-of-care ampicillin and gentamicin combination (AG) for treating Enterococcus faecalis IE, but other comparisons...
would have been hardly justifiable. Specifically, clinical data supporting the use of ampicillin monotherapy for this disease are weak, considering that isolated case reports are subject to publication bias, as generally, failures are not reported. Animal models, such as that of Thauvin et al [4], are very useful for establishing the rationale for further studies, but their findings have yet to be corroborated in humans. Vegetations in IE experimental models (created in 24–48 hours) differ considerably from those of patients, which usually develop over weeks, and antimicrobial performance may vary significantly depending on whether the target is planktonic or biofilm-embedded bacteria. Thus, additional studies are needed to resolve many remaining uncertainties: the efficacy of large doses of ampicillin in monotherapy (probably administered in continuous infusion), the stability of ampicillin solutions over 24 hours at room temperature, the dosage of ceftriaxone (2 g or 4 g/day), and the use of other antimicrobial combinations, such as ampicillin plus daptomycin [5] or ceftriaxone plus fosfomycin [6].

In their letter, Gelfand et al [1] also mention that it is difficult to compare the AC combination for treating *E. faecalis* IE with those of the presurgical era. Historical comparisons should be avoided in this case, not only because of potential bias related to technical improvements, but also because of the significant epidemiologic changes IE has undergone over the last decades [7].

Recent observational studies have shown that similar efficacy is reached with a short (2-week) and a complete (4-week) course of gentamicin [8, 9], with less renal damage in the first group. However, taking into account that the AC combination is not nephrotoxic and the fact that up to 25% of all *E. faecalis* strains in our study presented high-level aminoglycoside resistance [2], it is difficult not to support the use of AC as the first therapeutic option.

Finally, Gelfand et al alert to extended-spectrum β-lactamase (ESBL)-producing gram-negative bacilli (GNB) and *Clostridium difficile* infections secondary to the use of 2 β-lactams. In our personal experience at Vall d’Hebron Hospital, none of the 67 patients with *E. faecalis* IE treated with AC presented *C. difficile*-associated diarrhea (CDAD). Furthermore, in our study, similar rates of CDAD were found in AC- and AG-treated patients in whom this information was available: 3 of 142 in the AC group (2.1%), and 1 of 62 in patients receiving AG (1.6%) (*P* = .812). Regarding ESBL-producing GNB, surveillance cultures are not performed routinely, so this question remains unanswered. Fortunately, however, IE is an uncommon disease and use of the AC combination in a limited number of patients would represent a very small disturbance of microbiological ecology.

On the other hand, Solla raises an interesting methodological question regarding the design of our comparative study [10]. Superiority, equivalence, and noninferiority analyses make full sense in the context of randomized trials in which a statistical margin is established a priori. Due to its observational and retrospective nature, this is not the case in our study, but it is true that the level of uncertainty was not reported.

In our series, 18 of 87 (20.7%) patients receiving AG died while on treatment as compared to 35 of 159 (22.0%) patients receiving AC. To quantify the extent to which it is appropriate to state that both treatments are equivalent in terms of fatal event rates, we have computed a post hoc statistical power for equivalence. In the hypothesis test for equivalence of 2 mortality rates, we consider as the null hypothesis that there are differences in mortality during treatment between groups greater than a given equivalence limit (δ). Thus, in our case, for an equivalence hypothesis test, we may consider that the expected percentage of fatal events was that of AG-treated patients (20.7%), and δ as the observed difference between groups (−1.3%). Accepting an α risk of 0.05 in a 2-sided test, the power to reject the null hypothesis and accept the equivalence of proportions is 82%. The same methodology has been used in the case of mortality during follow-up, with a 77% power to accept the equivalence of proportions. Statistical analyses were performed with a SPSS macro developed by R. Granero and J.M. Domenech [11].

The statistical power for an equivalence test is closely related but conceptually different to the statistical power for the difference between 2 proportions. In this sense, in our study we would reach a statistical power of 80% to detect differences in mortality rates between both groups of >10%.

Thus, although we concluded that a randomized controlled trial should be performed to confirm our findings, we believe that our results are not invalidated by the statistical analysis used.

Notes

**Acknowledgments.** We thank Ignacio Ferreiragonzález and Aida Ribera for methodological support.

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Nuria Fernández-Hidalgo, Benito Almirante, and Albert Pahissa
Servei de Malalties Infeccioses, Hospital Universitari Vall d’Hebron, Universitat Autònoma de Barcelona, Spain

References