Effectiveness of Ampicillin Plus Ceftriaxone Compared to Ampicillin Plus Gentamicin for Treating Enterococcus faecalis Infective Endocarditis: A Noninferiority Question Not Yet Properly Investigated

To the Editor—I read with interest the article by Fernández-Hidalgo et al, comparing the effectiveness of the ampicillin plus ceftriaxone (AC) and ampicillin plus gentamicin (AG) combinations for treating Enterococcus faecalis infective endocarditis (EFIE) [1].

Although I recognize the clinical usefulness of this effort, in a field with limited therapeutic alternatives, I believe that the current evidence regarding AC versus AG treatment for EFIE does not support the conclusion that AC is as effective as AG in terms of mortality. I should note that this study had a superiority design, but aimed to claim for noninferiority—an inadequate approach [2–4]. A more comprehensive interpretation of the results would require a careful evaluation of the confidence intervals regarding the difference in mortality, not only the point estimates. This is of greater relevance given the relative small sample and limited statistical power. From the published data in the article’s Table 3, we can obtain the information shown in Table 1.

Indeed, one cannot rule out, with adequate confidence, the null hypothesis that the mortality for AC treatment is equal (0% difference) to that of the AG treatment (this is the reason why the P value was nonsignificant). But, in the same way, all other values covered by the confidence interval cannot be rejected [5], and we cannot conclude that the AC treatment mortality is not 5, 10, or even 13.5 percentage points higher for death during treatment or 5, 10, or even 16.7 percentage points higher for death until 3 months compared to AG treatment. Thus, there is a considerable uncertainty in this comparison and to conclude that the treatments are similar would be inadequate. Moreover, to change the current recommendations regarding EFIE treatment, notably for non–high-level aminoglycoside resistance strains, may be imprudent.

Future clinical trials aiming to investigate alternative treatment strategies for ampicillin plus gentamicin in EFIE should consider an equivalence or noninferiority design [6]. At this point, the researchers would have to set a margin of clinical noninferiority considering a risk-benefit ratio that accounts for renal dysfunction (either transitory or not) and relapses, for example. Other unanswered questions posed by the accompanying editorial to Fernández-Hidalgo et al’s article could also be clarified [7].

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has 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.

Table 1. Death Outcomes of 246 Episodes of Enterococcus faecalis Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin a

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amp-Cef (n = 159)</th>
<th>Amp-Genta (n = 87)</th>
<th>Absolute Difference (%)</th>
<th>Relative Difference (Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death during treatment</td>
<td>n = 35, 22.0 (15.3–30.6)</td>
<td>n = 18, 20.7 (12.3–32.7)</td>
<td>1.3 (–10.8 to 13.5)</td>
<td>1.06 (.59–2.00)</td>
</tr>
<tr>
<td>Death until 3 mo</td>
<td>n = 48, 30.2 (22.5–40.0)</td>
<td>n = 24, 27.6 (17.7–41.1)</td>
<td>2.6 (–11.5 to 16.7)</td>
<td>1.09 (.66–1.87)</td>
</tr>
</tbody>
</table>

All data are presented with the respective 95% confidence interval. Abbreviations: Amp, ampicillin; Cef, ceftriaxone; Genta, gentamicin.

a Adapted from Fernández-Hidalgo et al [1].

References


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