Comment on: Glycopeptide use is associated with increased mortality in Enterococcus faecalis bacteraemia

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Sir, Recently, Foo et al.1 published a study on Enterococcus faecalis bacteraemia and the dependence of the outcome on which antibiotic was used. In their analysis, glycopeptide use was associated with increased mortality in patients with E. faecalis bacteraemia. Several considerations must be discussed about this issue.

Some characteristics of the presented cases of E. faecalis bacteraemia may have affected the results of the study. Firstly, glycopeptide-treated patients were more likely to have a healthcare-associated bacteraemia (67.4% in the glycopeptide group versus 46.6% in the β-lactam group; P = 0.013). Other concomitant antibiotics may have been employed, mainly in cases of polymicrobial episodes, but they are not reported by the authors and their possible impact on the study results is unknown.

We previously performed a 7 year study in a similar manner to the Foo et al.1 study, focusing on risk factors, clinical features and outcomes in patients with bacteraemia caused by E. faecalis and Enterococcus faecium.2,3 In our study we collected data on the severity of illness calculated using the Simplified Acute Physiology Score II (SAPS II),4 comorbidities, inpatient antibiotic use and other treatment 30 days prior to bacteraemia, treatment (adequate antibiotic choice) and 30 day mortality, among other variables. Here we present the results of our cases of E. faecalis bacteraemia and we believe it could be useful to briefly compare our study with that of Foo et al.1 A total of 153 episodes of E. faecalis bacteraemia were included in our study.

Univariate analyses were performed using the χ2 or Fisher’s exact test for categorical variables and Student’s t-test or the Mann–Whitney U-test for continuous variables. Predictors of the mortality of patients with E. faecalis bacteraemia were assessed using logistic regression models. All variables significant at a P value of <0.20 in univariate analyses were included in a multi-variable logistic regression model. Multivariable logistic regression analysis (Table 1) showed that healthcare-associated bacteraemia, mechanical ventilation, SAPS II > 30, previous chemotherapy treatment for cancer, >15 days of intensive care unit (ICU) stay and renal insufficiency were associated with 30 day mortality. Like Foo et al.,1 we analysed the relationship between malignancy and 30 day mortality. However, we classified episodes of E. faecalis bacteraemia into oncological and haematological diseases and whether the patient underwent previous antineoplastic chemotherapy. In our study, this last factor was statistically associated with 30 day mortality. Other conorbidities were found to be predictors of mortality in the two studies; in our study renal insufficiency was such a predictor. Each study employed different surrogate markers of disease severity (APACHE II and SAPS II) and all were associated with mortality in E. faecalis bacteraemia. However, an association between glycopeptide therapy and mortality was not observed in our study [dead, n = 6/31 (19.4%); alive, n = 29/122 (23.8%); P = 0.601]. Of note, in the Foo et al.1 study, patients with glycopeptide therapy had healthcare-associated infection more frequently than those without glycopeptide therapy, and this characteristic was related to mortality.

Importantly, we also found that healthcare-associated infection was associated with mortality. In accordance with this finding, more days of stay in ICU and mechanical ventilation were related to decreased survival.

In conclusion, the variability noted in both studies highlights the need to develop further prospective studies determining more variables that could affect mortality and to understand the clinical significance of E. faecalis bacteraemia.

Table 1. Multivariate logistic regression model of factors associated with 30 day mortality in E. faecalis bacteraemia of our study

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare associated</td>
<td>5.74</td>
<td>1.12–29.33</td>
<td>0.036</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3.21</td>
<td>0.98–10.54</td>
<td>0.054</td>
</tr>
<tr>
<td>SAPS II &gt; 30</td>
<td>3.40</td>
<td>1.20–9.65</td>
<td>0.022</td>
</tr>
<tr>
<td>Length of stay in ICU (&gt;15 days)</td>
<td>12.28</td>
<td>2.43–62.13</td>
<td>0.002</td>
</tr>
<tr>
<td>Chemotherapy treatment for cancer</td>
<td>3.40</td>
<td>1.00–11.54</td>
<td>0.050</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.58</td>
<td>0.87–7.63</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Transparency declarations
None to declare.

References
Letters to the Editor

Glycopeptide use is associated with increased mortality in Enterococcus faecalis bacteraemia—authors’ response

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Keywords: vancomycin, β-lactams, ampicillin, healthcare-associated bacteraemia

Sir,

We thank Conde-Estevez and Grau1 for their interest in our study.2 They go on to present a re-analysis of Enterococcus faecalis bacteraemic episodes derived from subsets of two previously published papers,3,4 examining factors associated with overall 30 day mortality.

Several independent variables for outcomes were observed and corresponded closely with our study. These included surrogates for more severe illness: Simplified Acute Physiological Score II (SAPS II) and need for mechanical ventilation or ICU stay for >15 days. In addition, similar to our study, healthcare-associated episodes had worse outcomes.

In contrast, Conde-Estevez and Grau1 were unable to replicate our main finding—that glycopeptide therapy was associated with patient mortality in β-lactam-susceptible Enterococcus faecalis bacteraemia.2 There are several possible explanations for this. Firstly, the number of glycopeptide-treated episodes was lower (22.9%; 35/153) than in our study (26.7%; 46/172) and thus may be below the threshold required to detect this association. Secondly, overall patient management has likely improved with time, as suggested by the reduced mortality in our study: 15.1% (between 2006 and 2013) compared with 20.2% (between 2000 and 2006) in their cohort. Consequently, the impact of therapy becomes more noticeable in later studies due to fewer confounders. Finally, the impact of glycopeptide therapy may be E. faecalis strain dependent.

It should be noted that, in our study, patients who received both a β-lactam and a glycopeptide agent were excluded. Furthermore, all attempts to correct for a possible selection bias were made, including using a propensity score-based analysis. Nevertheless, Conde-Estevez and Grau1 correctly point out the possible impact of concomitant antibiotics, which were used predominantly in the case of polymicrobial bacteraemias and/or intra-abdominal infections in our study. In many of these cases, monotherapy with piperacillin/tazobactam was employed due to its additional Gram-negative and anaerobic cover, and these patients were therefore included in the β-lactam treatment group. In other cases, the concomitant antibiotic was an agent without significant anti-enterococcal cover (e.g. quinolones, cephalosporins, fluoroquinolones), and therefore considered unlikely to have any significant impact on study outcomes. Combination therapy with an aminoglycoside was employed in 18 patients (most of whom had endocarditis). Although aminoglycosides may have synergistic benefits when used in combination with β-lactam agents, in our study the numbers were too small to detect an independent association with outcome.

We agree with Conde-Estévez and Grau1 regarding the need for more research in this important area. However, based on our data, we would no longer recommend a glycopeptide as first-line therapy in the management of β-lactam-susceptible E. faecalis bacteraemia.

Transparency declarations

None to declare.

References