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LETTER TO THE EDITOR

Outcomes of Patients with Bloodstream Infections Caused by Ampicillin-Susceptible but Penicillin-Resistant *Enterococcus faecalis*: Caution in Interpreting the Results

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We read with great interest the article by Kim et al. published in *Antimicrobial Agents and Chemotherapy* on the clinical prognoses of ampicillin-susceptible but penicillin-resistant (ASPR) *Enterococcus faecalis* infections (1). This phenotype appeared to confer an increased risk of 30-day mortality among patients with *E. faecalis* bloodstream infections (BSI), particularly those treated with ampicillin (AMP) or piperacillin-tazobactam (TZP). The findings raised concern for an increased risk of mortality despite the use of appropriate therapy guided by *in vitro* susceptibilities.

We believe that uncertainties in this study make the results difficult to interpret. First, piperacillin (PIP) or TZP *in vitro* susceptibilities of study isolates were not reported, likely as the Clinical and Laboratory Standards Institute accepts AMP *in vitro* susceptibility as a surrogate for non-β-lactamase-producing isolates (2). However, a concerning rate of discordance between these susceptibility phenotypes has been described. Conceição et al. reported on 34 non-β-lactamase-producing ASPR *E. faecalis* isolates, of which 9 were susceptible to PIP by disk diffusion but none were by broth dilution (BD) or gradient strip testing (3). Similarly, Tan et al. reported that among 3 *E. faecalis* isolates confirmed to be ASPR, 2 isolates were found to have PIP resistance (by broth microdilution and gradient strip testing) (4). All isolates were negative for β-lactamase production. Furthermore, Infante et al. found that among 21 ASPR *E. faecalis* isolates, 19% were resistant to PIP (BD and disk diffusion) and an amino acid substitution (D573E) was identified in PBP4 (5). Conceivably, *pbp4* mutations associated with the ASPR phenotype may contribute to PIP resistance, though this has yet to be directly investigated. These findings cast doubt on the reliability of *in vitro* AMP susceptibility as a surrogate marker for TZP.

Second, patients who received AMP or TZP were combined into one group. In this group, patients with ASPR isolates had increased mortality compared to that of patients infected with a non-ASPR isolate. This difference was not observed among patients treated with glycopeptide-containing regimens. These results raise the possibility that the ASPR phenotype was associated with a poor clinical response to β-lactams even if their administration was deemed appropriate by *in vitro* susceptibility testing. However, it is crucial to specify the number of patients treated with TZP rather than ampicillin, as

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it is possible that TZP was an inactive therapy but not correctly identified as such by *in vitro* AMP susceptibility testing.

Third, combined ampicillin and ceftriaxone therapy is the regimen favored by many clinicians to treat serious high-inoculum BSI caused by *E. faecalis* (6). In the study by Kim et al., arguably lower-risk sources of BSI (e.g., urinary tract [11.2%], central line [1.7%]) comprised only a small fraction of the cohort. Notably, 33.9% of patients required intensive care (1). With serious infections, rates of combination therapy and specific second agents used in patients who received AMP or TZP without a glycopeptide versus those who received glycopeptide-containing regimens are important data for interpreting the results.

Kim et al. raise an important clinical question. However, conclusions need to be taken with caution, and further data are required to support the findings and optimize the treatment and clinical care of patients infected with these organisms.

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