Impact of MIC of piperacillin/tazobactam in the outcome of patients with bacteremia due to extended-spectrum \( \beta \)-lactamase-producing *Escherichia coli*

Running title: Piperacillin/tazobactam MIC in invasive ESBL-*E. coli*

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ABSTRACT

We investigated the impact of piperacillin/tazobactam MIC in the outcome of 39 bloodstream infections due to extended-spectrum β-lactamase-producing Escherichia coli. All 11 patients with urinary tract infections survived irrespective of the MIC. For other sources, 30-day mortality was lower for isolates with MIC ≤ 2 mg/L than for higher MIC (0 vs. 41.1%, p=0.02).
Carbapenems are considered the drugs of choice for treating severe infections caused by extended-spectrum $\beta$-lactamase (ESBL)-producing Enterobacteriaceae (1). There is an increasing interest in investigating potential alternatives to these drugs because of the spread of carbapenemase-producing organisms. Recently, in a post-hoc analysis of prospective cohorts, we showed that $\beta$-lactams/$\beta$-lactam inhibitor combinations (BLBLI) including amoxicillin-clavulanate and piperacillin-tazobactam (PTZ) showed similar efficacy than carbapenems in treating bloodstream infections (BSI) due to susceptible ESBL-producing Escherichia coli (ESBLEC) (2). The objective of this study was to analyse the impact of the minimum inhibitory concentrations (MIC) of PTZ, and of other variables, on the outcome of patients with BSI due to ESBLEC, treated empirically with this antibiotic.

Cases included in this analysis were selected from a merged database of 6 previously reported prospective cohorts of adult (>17 years) patients with BSI due to ESBLEC; the characteristics of the cohorts and an analysis comparing patients treated with BLBLI and carbapenems when active in vitro have been previously reported (2). Here, all patients treated from those cohorts treated with PTZ irrespective of the MIC of the isolate were included (resistant isolates were excluded from the previous report (2)) provided that: (a) bacteremia was monomicrobial, along with criteria for sepsis; (b) the patients received empirical monotherapy with PTZ; and (c) the first PTZ dose was administered intravenously within the first 24 hours after the blood culture was drawn. The study was approved by the Ethics Committee of the Hospital Universitario Virgen Macarena, Seville. The microbiological studies carried out have been published previously (2). Susceptibility testing was performed by microdilution. Isolates showing a MIC of PTZ ≤8 mg/L were considered susceptible according to EUCAST (3); also,
for the purpose of this analysis, the isolates were classified as showing “high MIC” (non-susceptible isolates or MIC $\geq 16$ mg/L), “intermediate MIC” (4–8 mg/L), and “low MIC” ($\leq 2$ mg/L) (Figure 1). The main outcome variable was all-cause 30-day mortality.

More than 90% of the patients received intravenously 4,500 mg of PTZ every 6 hours. Comparisons of percentages were performed by Fisher’s exact test (2-tailed).

Thirty-nine patients with bacteremia due to ESBL EC received empirical monotherapy with PTZ and were included. Eighteen isolates (46.1%) showed a low MIC ($\leq 2$ mg/L), 10 (25.6%) an intermediate (4–8 mg/L), and 11 (28.2%) a high MIC ($>8$ mg/L). All-cause 30-day mortality was 17.9% (7 patients). The features of the patients according to the MIC are shown in Table S1 (Supplemental Material); while there were not statistically significant differences among the 3 groups in demographic features, nosocomial acquisition, severity of underlying disease according to Charlson index, source, or presentation with severe sepsis/septic shock, it should be noted that numbers were low and that patients infected with high MIC isolates somehow showed more frequently a Charlson index $>2$.

Mortality according to exposure to various characteristics of the patients is shown in the Table and Figure. When all patients were considered irrespective the MIC, only presentation with severe sepsis or shock was associated with increased mortality. Regarding the MIC subsets, no patient with low MIC died. Mortality was lower among patients with low MIC when compared with those with high MIC. Mortality was also significantly higher for high MICs than for low and intermediate MIC combined (57.1% vs. 57.1%; RR=0.21; 95% CI: 0.06–0.75; p=0.01) and also for intermediate and high MIC combined than for low MIC (41.1% vs. 0; RR=0.13; 95% CI: 0.01–0.98; p=0.002).

None of the 11 patients with a urinary tract source died, irrespective of MIC. Among patients with non-urinary tract sources, mortality was lower among patients with low
MIC. The features of the patients who died are shown in Table S2 (Supplement Material).

The availability of a merged database that included prospective cohorts of patients with BSI infections due to ESBL E. coli who had been carefully followed, provided us with the opportunity to investigate the influence of MIC and other variables on the outcome of patients who received empirical treatment with PTZ. Our results show that the mortality of patients treated empirically with high doses of PTZ correlated with MIC values and that those patients with a low MIC (≤2 mg/L) had significantly lower mortality. We chose this particular ‘breakpoint’ because it is the mode MIC for wild-type E. coli, and 85% of wild-type isolates had MICs of ≤2 mg/L (4).

These data however should be interpreted alongside other variables that influence mortality in patients with BSI, such as source of infection or severity of SIRS at presentation (5). Since collecting high number of cases with different MICs treated with a specific antimicrobial is difficult, control for confounding is challenging. Multivariate analysis was not possible due to low numbers, so we performed a stratified analysis in order to give some insights into the impact of these variables on MIC categories. From this analysis, a few data may be mentioned. First, there was no mortality among patients with urinary tract infections treated with PTZ irrespective of the MIC. Secondly, mortality was higher in patients with intermediate and high MICs of PTZ with BSI from other sources. Finally, stratification by severity of SIRS at presentation (or any other variable) did not seem to strongly modify the relationship between MIC and mortality.

We previously showed that empirical or definitive therapy with active BLBLI (including PTZ and amoxicillin/clavulanate) showed similar mortality and hospital stay as carbapenems in patients with BSI due to susceptible ESBL E. coli (3). In that study, we
stated that the results were applicable mainly to patients with bacteremia from the urinary tract because that was the dominant source. In addition, Gavin et al found that PTZ cured 13 patients with urinary tract infections irrespective of MIC, although they did not specify whether or not the infections were bacteremic (6). This is probably due to the high concentrations reached by these antibiotics in the urine, and to the fact that urinary tract bacteremic infections are associated with lower mortality rates (5). However, we do not advocate empirical monotherapy with PTZ for patients with urinary tract sepsis in any context of moderate to high resistance rate to these antibiotics.

Our results also suggest that PTZ may be safely used in bacteremia from some non-urinary tract sources at least if the MIC is low enough (≤2 mg/L); most of the patients in this category had intra-abdominal infections, so that this may apply only to this particular source, in which appropriate surgical therapy is frequently key. More studies would be required for isolates with MICs of between 4 and 8 mg/L because the few patients with such isolates had similar mortality rates when compared to those with resistant isolates. This contrasts with Gavin et al results, who found that 8 patients with non-urinary tract infections (sites and invasive condition not specified) caused by ESBL-producing E. coli or Klebsiella spp. and showing MIC values of 4 or 8 mg/L, were cured with this antimicrobial (6). It is noted that the PTZ CLSI breakpoint for susceptibility against Enterobacteriaceae is ≤16 mg/L (7) while the EUCAST is ≤8 mg/L (3), according to data from some pharmacokinetic-pharmacodynamic models (8). Our study has several limitations. The statistical power of the study was limited because of the low numbers involved, and was also insufficient to carry out more suitable analyses for identifying PTZ MIC values that are predictive of treatment outcome, such as a classification and regression tree (CART) analysis or a multivariate
analysis with different breakpoints. The data may not be applicable to enterobacteria other than *E. coli*. Finally, the effect of other aspects of management or confounders could not be studied.

In summary, our results suggest that PTZ is effective for treating urinary tract bacteremia caused by ESBL-EC. For other sources, particularly intra-abdominal infections, PTZ showed better results against isolates showing a low MIC.

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Figure. Mortality of patients with bacteremia due to ESBL-producing *Escherichia coli* treated empirically with piperacillin/tazobactam, according to source and MIC.

aOne had severe sepsis/shock (survived). bOne had severe sepsis/shock (survived). cTwo had severe sepsis/shock (one died). dThree had severe sepsis/shock (two died).
Table. Mortality among patients with bacteremia due to ESBL-producing *E. coli* treated empirically with piperacillin/tazobactam, according to MIC and other variables of interest. Data are expressed as number of patients who died/number of patients in each category (percentage).

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=39)</th>
<th>Low MIC (≤2 mg/L) (n=18)</th>
<th>Intermediate MIC (4-8 mg/L) (n=10)</th>
<th>High MIC (≥16 mg/L) (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>7/39 (17.9)</td>
<td>0/18 (0)</td>
<td>3/10 (30)</td>
<td>4/7 (57.1)</td>
</tr>
<tr>
<td>Age ≤65 years</td>
<td>4/20 (20)</td>
<td>0/9 (0)</td>
<td>1/5 (20)</td>
<td>3/6 (50)</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>3/19 (15.8)</td>
<td>0/9 (0)</td>
<td>2/5 (40)</td>
<td>1/5 (20)</td>
</tr>
<tr>
<td>Onset Community</td>
<td>2/21 (9.5)</td>
<td>0/10 (0)</td>
<td>1/5 (20)</td>
<td>1/6 (16.7)</td>
</tr>
<tr>
<td>Onset Nosocomial</td>
<td>5/18 (27.8)</td>
<td>0/8 (0)</td>
<td>2/5 (40)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Charlson index ≤2</td>
<td>4/24 (16.7)</td>
<td>0/12 (0)</td>
<td>3/8 (37.5)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>Charlson index &gt;2</td>
<td>3/15 (20)</td>
<td>0/6 (0)</td>
<td>0/2 (0)</td>
<td>3/7 (42.9)</td>
</tr>
<tr>
<td>Source Urinary tract</td>
<td>0/11 (0)</td>
<td>0/7 (0)</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Source Others</td>
<td>7/28 (25)</td>
<td>0/11 (0)</td>
<td>3/8 (37.5)</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>Severe sepsis or shock No</td>
<td>4/32 (12.5)</td>
<td>0/16 (0)</td>
<td>2/8 (25)</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>Severe sepsis or shock Yes</td>
<td>3/7 (42.8)</td>
<td>0/2 (0)</td>
<td>1/2 (50)</td>
<td>2/3 (66.7)</td>
</tr>
<tr>
<td>Definitive therapy PTZ</td>
<td>0/10</td>
<td>0/5 (0)</td>
<td>0/4 (0)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Definitive therapy Carbapenem</td>
<td>5/24 (20.8)</td>
<td>0/10 (0)</td>
<td>1/4 (25)</td>
<td>4/10 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>0/3 (0)</td>
<td>0/3 (0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PTZ: piperacillin/tazobactam. *Only patients who survived long enough to receive definitive therapy were included. Other sources included biliary tract (6), unknown and spontaneous peritonitis (2 each), and secondary peritonitis (1) for low MIC; biliary tract (4), respiratory tract, skin and skin structure, catheter, unknown (1 each) for intermediate MIC; and biliary tract (3), skin and skin structure, spontaneous peritonitis (2 each), respiratory tract, secondary peritonitis (1 each) for high MIC.

P values (Fisher’s test; only those <0.1 are shown): aLow MIC vs intermediate MIC: 0.08; bLow MIC vs. high MIC: 0.005; cLow MIC vs intermediate MIC: 0.05; dLow MIC vs high MIC: 0.02; *presentation without vs. with severe sepsis or shock: 0.09.