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Impact of the MIC of Piperacillin-Tazobactam on the Outcome of Patients with Bacteremia Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

Pilar Retamar,[a] Lorena López-Cerero,[a] Miguel Angel Muniain,[a,b] Álvaro Pascual,[a,c] Jesús Rodríguez-Baño,[a,b] the ESBL-REIPI/GEIH Group

Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Sevilla, Spain[a]; Departamento de Medicina[b] and Departamento de Microbiología,[c] Universidad de Sevilla, Sevilla, Spain

We investigated the impact of the 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 a MIC of ≤2 mg/liter than for isolates with a higher MIC (0% versus 41.1%; $P = 0.02$).

Carbapenems are considered the drugs of choice for treating severe infections caused by extended-spectrum-β-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 β-lactam/β-lactam inhibitor combinations (BLBLI), including amoxicillin-clavulanate and piperacillin-tazobactam (PTZ), showed efficacy similar to that of carbapenems in treating bloodstream infections (BSI) due to susceptible ESBL-producing *Escherichia coli* (ESBLEC) (2). The objective of this study was to analyze the impact of the MICs 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-year-old) 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 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 (i) bacteremia was monomicrobial, along with criteria for sepsis, (ii) the patients received empirical monotherapy with PTZ, and (iii) the first PTZ dose was administered intravenously within the first 24 h after the blood culture was drawn. The study was approved by the Ethics Committee of the Hospital Universitario Virgen Macarena, Sevilla, Spain. The microbiological studies carried out have been published previously (2). Susceptibility testing was performed by microdilution. Isolates showing a PTZ MIC of ≤8 mg/liter were considered susceptible according to EUCAST (3); also, for the purpose of this analysis, the isolates were classified as showing "high MIC" (nonsusceptible isolates or a MIC of ≥16 mg/liter), "intermediate MIC" (4 to 8 mg/liter), and "low MIC" (≤2 mg/liter) (Fig. 1). The main outcome variable was all-cause 30-day mortality. More than 90% of the patients received 4,500 mg of PTZ intravenously every 6 h. Comparisons of percentages were performed by Fisher's exact test (2-tailed).

Thirty-nine patients with bacteremia due to ESBLEC received empirical monotherapy with PTZ and were included. Eighteen isolates (46.1%) showed a low MIC (≤2 mg/liter), 10 (25.6%) showed an intermediate MIC (4 to 8 mg/liter), and 11 (28.2%) showed a high MIC (>8 mg/liter). All-cause 30-day mortality was 17.9% (7 patients). The features of the patients according to the MIC are shown in Table S1 in the supplemental material; while there were not statistically significant differences among the 3 groups in demographic features, nosocomial acquisition, severity of underlying disease according to the 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 of >2.

Mortality according to exposure to various characteristics of the patients is shown in Table 1 and Fig. 1. When all patients were considered, irrespective of the MIC, only presentation with severe sepsis or shock was associated with increased mortality. Regarding the MIC subsets, no patient with a low-MIC isolate died. Mortality was lower among patients with a low-MIC isolate than those with a high-MIC isolate. Mortality was also significantly higher for high MICs than for low and intermediate MICs combined (57.1% versus 57.1%; relative risk [RR] = 0.21; 95% confidence interval [CI], 0.06 to 0.75; $P = 0.01$) and for intermediate and high MICs combined than for low MICs (41.1% versus 0%; RR = 0.13; 95% CI, 0.01 to 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 isolates. The features of the patients who died are shown in Table S2 in the supplemental material.

The availability of a merged database that included prospective cohorts of patients with BSI infections due to ESBLEC who had

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Address correspondence to Jesús Rodríguez-Baño, jesusrb@us.es.

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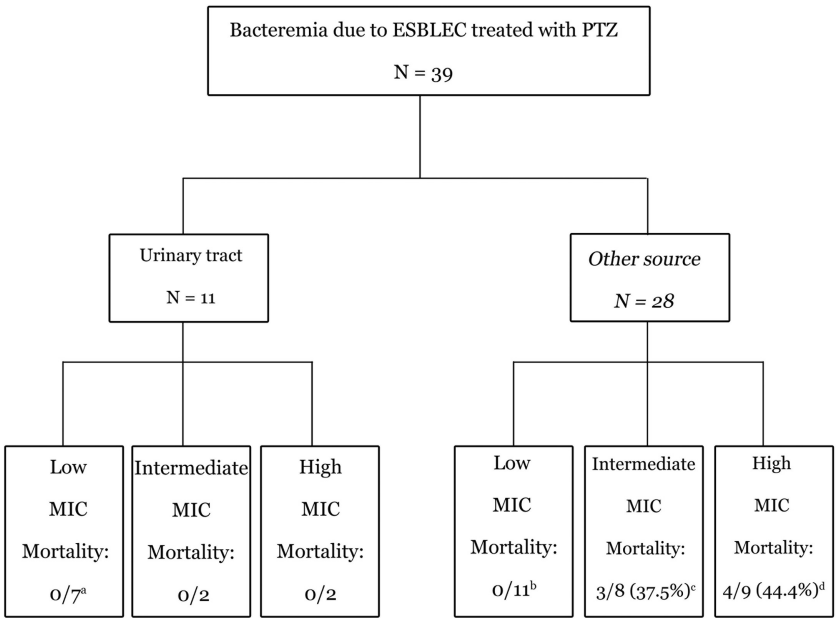

FIG 1 Mortality of patients with bacteremia due to ESBL-producing *Escherichia coli* treated empirically with piperacillin-tazobactam, according to source and MIC. [a]One had severe sepsis/shock (survived). [b]One had severe sepsis/shock (survived). [c]Two had severe sepsis/shock (one died). [d]Three had severe sepsis/shock (two died).

been carefully followed provided us with the opportunity to investigate the influence of the 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/liter) 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/liter (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 systemic inflammatory response syndrome (SIRS) at presentation (5). Since collecting a high number of cases with different MICs treated with a specific antimicrobial is difficult, controlling for confounders is challenging. Multivariate analysis was not possible due to low numbers, so we performed a stratified analysis in order to give some insight 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. Second, mortality was higher in patients with intermediate and high MICs of PTZ against 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 mortality and hospital stay similar to those of carbapenems in patients with BSI due to susceptible ESBLEC (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 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/liter); most of the patients in this category had intra-abdominal infections, so this may apply only to this particular source, in which appropriate surgical therapy is frequently key. More studies are required for isolates with MICs between 4 and 8 mg/liter because the few patients with such isolates had mortality rates similar to those with resistant isolates. This contrasts with the results of Gavin et al., 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/liter were cured with this antimicrobial (6). It is noted that the CLSI PTZ breakpoint for susceptibility against *Enterobacteriaceae* is ≤16 mg/liter (7) while the EUCAST breakpoint is ≤8 mg/liter (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 was not able to be studied.

In summary, our results suggest that PTZ is effective for treating urinary tract bacteremia caused by ESBLEC. For other sources,

TABLE 1 Mortality among patients with bacteremia due to ESBL-producing *E. coli* who were treated empirically with piperacillin-tazobactam, according to MIC and other variables of interest

Variable and group	Mortality in patients in each group[a]			
	All patients ($n = 39$)	Low MIC (≤2 mg/liter) ($n = 18$)	Intermediate MIC (4 to 8 mg/liter) ($n = 10$)	High MIC (≥16 mg/liter) ($n = 11$)
All patients	7/39 (17.9)	0/18 (0)[b]	3/10 (30)	4/7 (57.1)
Age				
≤65 years	4/20 (20)	0/9 (0)	1/5 (20)	3/6 (50)
>65 years	3/19 (15.8)	0/9 (0)	2/5 (40)	1/5 (20)
Onset				
Community	2/21 (9.5)	0/10 (0)	1/5 (20)	1/6 (16.7)
Nosocomial	5/18 (27.8)	0/8 (0)	2/5 (40)	3/5 (60)
Charlson index				
≤2	4/24 (16.7)	0/12 (0)	3/8 (37.5)	1/4 (25)
>2	3/15 (20)	0/6 (0)	0/2 (0)	3/7 (42.9)
Source				
Urinary tract	0/11 (0)	0/7 (0)	0/2 (0)	0/2 (0)
Other	7/28 (25)	0/11 (0)[c]	3/8 (37.5)	4/9 (44.4)
Severe sepsis or shock				
No	4/32 (12.5)[d]	0/16 (0)	2/8 (25)	2/8 (25)
Yes	3/7 (42.8)	0/2 (0)	1/2 (50)	2/3 (66.7)
Definitive therapy[e]				
PTZ	0/10	0/5 (0)	0/4 (0)	0/1 (0)
Carbapenem	5/24 (20.8)	0/10 (0)	1/4 (25)	4/10 (40)
Other	0/3 (0)	0/3 (0)		

[a] Data are expressed as number of patients who died/number of patients in each category (percentage). PTZ, piperacillin-tazobactam.
[b] Low MIC versus intermediate MIC, $P = 0.08$; low MIC versus high MIC, $P = 0.005$. P values were obtained by Fisher's test; only those <0.1 are shown.
[c] Low MIC versus intermediate MIC, $P = 0.05$; low MIC versus high MIC, $P = 0.02$. P values were obtained by Fisher's test; only those <0.1 are shown.
[d] Presentation without versus with severe sepsis or shock, $P = 0.09$. P values were obtained by Fisher's test; only those <0.1 are shown.
[e] 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) and respiratory tract, skin and skin structure, catheter, and unknown (1 each) for intermediate MIC, and biliary tract (3), spontaneous peritonitis and skin and skin structure (2 each), and respiratory tract and secondary peritonitis (1 each) for high MIC.

particularly intra-abdominal infections, PTZ showed better results against isolates showing a low MIC.

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