

Update on antimicrobial pharmacotherapy against multidrug-resistant Gram-negative bacilli

Emilio Maseda¹
Alejandro Suárez de la Rica²

Controversies in the management of ESBL-producing *Enterobacterales*. Clinical Implications

¹Hospital La Paz. Hospital Quirón Torrejón. Madrid, Spain

²Hospital La Paz. Madrid, Spain

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ABSTRACT

Extended-spectrum β -lactamases (ESBL)-producing organisms currently represent a major health problem. Although recently published guidelines still consider carbapenems as the treatment of choice for ESBL-producing infections, it is necessary to find non-carbapenem β -lactams as alternatives to reduce the effects associated with their overutilization.

In this review we focus on these alternatives to carbapenem use. It is possible that piperacillin-tazobactam may be an alternative in clinical settings with "low inoculum" infections like urinary tract infections. Newer β -lactam- β -lactamase inhibitors (BLBLIs) are potential options too. The current available data support the efficacy of both ceftazidime-avibactam and ceftolozane-tazobactam against susceptible ESBL-producing *Enterobacterales* (ESBL-E). We are waiting for the results of MERINO-3 study to confirm whether ceftolozane-tazobactam is a good option versus meropenem for treating bloodstream infections caused by ESBL- or AmpC-producing *Enterobacterales*.

Keywords: Extended-spectrum β -lactamases, *Enterobacterales*, management

Extended-spectrum β -lactamases (ESBL) offer resistance to penicillins and cephalosporins. ESBLs are present in several gram-negative organisms, being more prevalent among *Enterobacterales* such as *Escherichia coli* and *Klebsiella species*. ESBL-producing *Enterobacterales* (ESBL-E) were described in the 1980s and they currently represent a global crisis [1-3].

The progressive and worrying appearance in recent years of microorganisms resistant to carbapenems linked, among other causes, to carbapenem overuse has highlighted the need to assess the use of other non-carbapenem β -lactams as therapeutic alternatives to treat infections caused by ESBL-E.

However, the different recently published guidelines continue to consider carbapenems as the antibiotics of choice for the treatment of ESBL-causing infections [4-6] as they are stable to ESBL hydrolytic activity and offer favorable results on their clinical efficacy in different studies [7].

In this brief review, we will assess the available data on the use of non-carbapenem β -lactams as therapeutic alternatives to carbapenems for the treatment of ESBL-E producing infections, focusing on the use of piperacillin-tazobactam (PTZ) and the role of newer β -lactam- β -lactamase inhibitors (BLBLIs).

PIPERACILLIN-TAZOBACTAM (PTZ)

According to CLSI [8] and EUCAST [9], the breakpoints for PTZ are ≤ 16 mg/L $\gamma \leq 8$ mg/L, respectively. Although ESBLs are usually inhibited by β -lactamase inhibitors, ESBL-E may present resistance mechanisms to BLBLIs, because β -lactamases are not susceptible to inhibition due to the co-production of Amp-C or OXA-1 type enzymes, overproduction of ESBLs and/or mutations in permeability, and even by a possible "inoculum effect" demonstrated *in vitro*, in animal models and in clinical cases, which would affect PTZ above all [10,11].

Different observational studies have shown contradictory results in patients with infections caused by ESBL-E who were treated with PTZ and carbapenems. One of the initial works that evaluated the difference in mortality in treatment with BLBLIs and carbapenems in ESBL-E bacteremia was a *post hoc* observational study carried out in Spain on 6 cohorts of patients [12]. 70% of the bacteremia had a urinary or biliary origin ("low-inoculum" infections), and only 13% of the patients needed to be admitted to the intensive care unit (ICU). Thirty-day mortality was 10% and 19% in the empiric cohort and 9% and 17% in the definitive cohort for BLBLIs and carbapenems, respectively, although these differences did not reach statistical significance. In the Ofer-Friedman and colleagues'

Correspondence:
Emilio Maseda
Hospital La Paz. Madrid, Spain
E-mail: emilio.maseda@gmail.com

study, the mortality was compared between BLBLI and carbapenems for the treatment of ESBL bacteremia, excluding urinary sources [13]. Thirty-day mortality was 60% for the PTZ group and 34% for the carbapenem group, without statistical significance ($P = 0.10$).

According to these results, carbapenem therapy offers better results than PTZ therapy in critically ill patients with bacteremia caused by ESBL-E.

In another study conducted by Tamma et al., 14-day mortality of patients was compared between those who received PTZ and carbapenems as empiric therapy in a cohort of patients with ESBL bacteremia who all received definitive carbapenem therapy [14]. Only about 40% patients received 4.5 g every 6 h and no patients received extended-infusion therapy. The majority of patients had "high-inoculum" infections, one-third of patients required ICU care, and most ESBL isolates had elevated PTZ MICs. Thirty-day mortality was higher in the PTZ group than carbapenem group (17% vs 8%, $p < 0.05$).

However, there are several observational studies where no differences in mortality are obtained between the PTZ group and the carbapenem group. The study by Ng et al. was evaluated 30-day mortality in 151 patients with presumed ESBL bloodstream infections. There was no difference found in thirty-day mortality between the groups [15]. Gutiérrez-Gutiérrez et al. conducted a study comparing the effectiveness of BLBLIs and carbapenems for the treatment of ESBL bloodstream infections, including 365 patients in the empiric therapy group and 601 patients in the targeted therapy group [16]. The isolates were from urinary (45%) and biliary (12%) sources ("low-inoculum"). Mortality at 30 days was comparable between the study groups in both the empiric (18% BLBLI group vs 20% carbapenems group) and definitive cohorts (10% BLBLI group vs 14% carbapenems group).

A meta-analysis was performed comparing carbapenem and BLBLIs for ESBL bacteremia for both empiric and definitive therapies [7]. There was no difference in all-cause mortality between therapies. Sfeir et al. conducted a systematic review and meta-analysis comparing mortality between BLBLIs versus carbapenem for bloodstream infections due to ESBL-E [17]. There was no significant difference in 30-day mortality between BLBLI, including PTZ, and carbapenems in treating ESBL-E bloodstream infections. The authors concluded that BLBLI, especially PTZ, may be considered as an alternative treatment for ESBL-E bloodstream infections.

Nevertheless, it is still debatable whether BLBLIs can be considered for patients with ESBL-E producing infections. The MERINO trial compared PTZ to meropenem among patients with bloodstream infections due to 3rd generation cephalosporin-resistant *E. coli* and *K. pneumoniae* [18]. Primary outcome was 30-day mortality. The study did not prove the non-inferiority of PTZ, with 30-day mortality rates 12.3% with PTZ vs. 3.7% with meropenem, risk difference (RD) 8.6% (1-sided 97.5% CI, $-\infty$ to 14.5%). The RD was lower in the subgroup of patients with urinary tract infections (RD 3.7%, $-\infty$ to 10.7%) than among patients with other sources of bloodstream infec-

tions (RD 14.1%, $-\infty$ to 24.5%). Following the trial, the authors found a high rate of false susceptibility to PTZ among OXA-1 producers with automatic methods or strip-gradient test performed in the trial sites; 60% of isolates were OXA-1 and 10% Amp-C [19]. A further analysis of the trial excluded patients with bloodstream infections caused by non-susceptible strains (PTZ MIC > 16 mg/L; meropenem MIC > 1 mg/L CLSI, or MIC > 2 mg/L EUCAST). The between group difference in mortality decreased and was non-significant: 13/134 (9.7%) with PTZ versus 6/149 (4%) with meropenem; (RD 5.7%, -1 to 11). After excluding non-susceptible strains, the 30-day mortality difference from the MERINO trial was less pronounced for PTZ but according to the authors' conclusions the high prevalence of OXA cohabiting ESBLs suggests no recommendation in using PTZ for definitive treatment of ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella*.

The MERINO-2 was a pilot study comparing PTZ to meropenem among patients with bloodstream infections caused by presumed Amp-C β -lactamase producing but 3rd generation cephalosporin-susceptible *Enterobacter* spp., *Citrobacter freundii*, *Providencia* spp., *Klebsiella aerogenes*, *Morganella morganii* o *Serratia marcescens* [20]. Seventy patients were included. The difference between groups in clinical failure was no significant, 8/38 (21%) with PTZ vs. 4/34 (12%) with meropenem. There was significant difference between groups with respect to microbiological failure (5/38, 13% with PTZ versus 0/34, 0% with meropenem; $p = 0.03$), although fewer microbiological relapses were seen in the PTZ group (0/38, 0% with PTZ versus 3/34, 9% with meropenem; $p = 0.06$).

We are looking forward to seeing the MERINO-3 study. This study will use a multicentre, parallel group open-label non-inferiority trial design comparing ceftolozane-tazobactam and meropenem in adult patients with bloodstream infection caused by ESBL or AmpC-producing *Enterobacterales* [21].

Some authors consider that unfavorable outcomes with PTZ may be due to not using appropriate doses (4.5 g every 6 h or 8 h in continues or extended infusion). However, in a recent study there was no significant difference between patients with therapeutic drug monitoring (TDM) guided dose optimization of PTZ and without TDM in terms of 28-day mortality and clinical and microbiological cure [22].

NEWER BLBLIS (CEFTOLOZANE-TAZOBACTAM AND CEFTAZIDIME-AVIBACTAM)

Ceftazidime-avibactam is usually active against ESBL-E because of the inhibitory ability of avibactam on the ESBLs. A *post hoc* study showed the results from RECAPTURE 1 and 2 trials in ESBL-cases for complicated urinary tract infections comparing ceftazidime-avibactam and doripenem [23]. The clinical cure rates 91.7% and 88%, respectively. A systematic review and meta-analysis showed the results from ceftazidime-avibactam for serious infections due to ESBL- and Amp-C- producing *Enterobacterales* [24]. Clinical response was observed in 91% (224/246) of the patients with ESBL infections

in the ceftazidime-avibactam arm, versus 89% (240/271) of the patients in the carbapenem arm. In patients with Amp-C producing *Enterobacterales* (n=82), clinical response rates were 80% (32/40) and 88% (37/42) in the ceftazidime-avibactam and comparators arm, respectively. Microbiologic response for ceftazidime non-susceptible *Enterobacterales* was 85% in the ceftazidime-avibactam arm and 64% in the carbapenem group. Thus, ceftazidime-avibactam seems like a good option for the treatment of ESBL-E.

Ceftolozane-tazobactam is usually active against ESBL-E. The SUPERIOR multicenter study showed the activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* (n=80) and *Enterobacterales* (n=400) isolates recovered from intensive care unit patients with complicated urinary tract and complicated intra-abdominal infections in Spain [25]. The activity was excellent against wild-type organisms 100% susceptible. Nevertheless, ceftolozane-tazobactam susceptibility decreased against ESBL producers: *E. coli* (80.4% complicated intra-abdominal infection/84.8% urinary tract infection) and *Klebsiella pneumoniae* (59.1% complicated intra-abdominal infection/77.3% urinary tract infection). However, the clinical studies have shown good results against ESBL-E. In a pooled analysis of the pivotal clinical trials performed in patients with complicated urinary tract and intra-abdominal infections that included 2076 patients with 150 infected with ESBL-E [26] the clinical cure rates for patients with ESBL-producing *E. coli* and *K. pneumoniae* with ceftolozane-tazobactam were 98% (49/50) and 94.4% (17/18) respectively. The overall cure rates for complicated urinary tract infections with ceftolozane-tazobactam and levofloxacin against ESBL-E were 98.1% and 82.6%, respectively and for complicated intra-abdominal infection with ceftolozane-tazobactam plus metronidazole and meropenem were 95.8% and 88.5%, respectively. Bassetti et. evaluated ceftolozane-tazobactam for treatment of severe ESBL-E infections in a multicenter real-life study (CEFTABUSE II study) [27]. Ceftolozane-tazobactam treatment was documented in 153 patients: pneumonia was the most common diagnosis (n = 46, 30%), followed by 34 cases of complicated urinary tract infections (22.2%). Septic shock was observed in 42 (27.5%) patients. Favorable clinical outcome was observed in 128 (83.7%) and 30-day mortality was reported for 15 (9.8%) patients. Ceftolozane-tazobactam could be a valid option in empiric and/or targeted therapy in patients with severe infections caused by ESBL-E. Recently, Paterson et al. conducted a retrospective analysis of the ASPECT-NP clinical trial to confirm the efficacy of ceftolozane-tazobactam in treating hospital-acquired/ventilator-associated bacterial pneumonia due to ESBL-producing *Enterobacterales* [28]. The most frequent ESBL-positive and/or AmpC-overproducing *Enterobacterales* isolates (ceftolozane-tazobactam n=31, meropenem n=35) overall were *K. pneumoniae* (50.0%), *E. coli* (22.7%), and *Proteus mirabilis* (7.6%). Overall, 28-day all-cause mortality was 6.7% (2/30) with ceftolozane-tazobactam and 32.3% (10/31) with meropenem (25.6% difference, 95% CI: 5.54 to 43.84). Clinical cure rate at test-of-cure, 7–14 days after end of therapy, was 73.3% (22/30) with ceftolozane-tazobactam

and 61.3% (19/31) with meropenem (12.0% difference, 95% CI: –11.21 to +33.51). These data demonstrate that ceftolozane-tazobactam may be an appropriate option for treatment ESBL- and Amp-C-producing *Enterobacterales*.

Therefore, the available data support the efficacy of both new BLBLs against susceptible ESBL-E and both antibiotics could be an alternative to carbapenems. We are pending the results of MERINO-3 study to confirm whether ceftolozane-tazobactam is a good option versus meropenem for treating ESBL-producing infections.

CONCLUSIONS

Available data suggest that carbapenems should be the drug of choice for the treatment of ESBL-E severe infections. It is possible that in clinical settings with "low inoculum" infections like urinary tract infections, piperacillin-tazobactam may be an alternative. In fact, it is important to find non-carbapenem β -lactam for the treatment of ESBL-E to reduce the effects associated with their overuse. Newer BLBLs like ceftolozane-tazobactam and ceftazidime-avibactam are potential alternatives with good clinical results to date although we need more definitive data.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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