Carbapenem-Sparing Strategies for ESBL Producers

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Extended spectrum β-lactamase (ESBL)-producing bacteria are prevalent worldwide and correlated with hospital infections, but they have been evolving as an increasing cause of community acquired infections. The spread of ESBL constitutes a major threat for public health, and infections with ESBL-producing organisms have been associated with poor outcomes. Established therapeutic options for severe infections caused by ESBL-producing organisms are considered the carbapenems. However, under the pressure of carbapenem overuse and the emergence of resistance, carbapenem-sparing strategies have been implemented. The administration of carbapenem-sparing antibiotics for the treatment of ESBL infections has yielded conflicting results.

ESBLs piperacillin–tazobactam carbapenem-sparing treatment cefepime fosfomycin urinary tract infection

1. Introduction

The spread of extended spectrum β-lactamase (ESBL)-producing bacteria has increased the last two decades in the hospital setting as well as in the community, emerging as a serious threat of public health [1]. In particular, infections caused by antimicrobial-resistant *Escherichia coli* proportionally contributed the most to the burden of antimicrobial resistance in Europe, both as number of cases and number of attributable deaths [2]. The population-weighted mean rates of the third-generation cephalosporin resistance in 2018 were 13.1% and 31.7% for *E. coli* and *Klebsiella pneumoniae* isolates, respectively, in the EU and the European Economic Area [2]. ESBLs are enzymes that confer resistance to most beta-lactam antibiotics, including third-generation cephalosporins and monobactams, and they are often seen in combination with other resistance mechanisms, causing multidrug resistance [3]. The majority of ESBLs belong to Ambler class A and include the sulfhydryl reagent variable β-lactamase (SHV), Temoniera β-lactamase (TEM) and cefotaxime-M β-lactamase (CTX-M) types [3]. Infections caused by ESBL-producing Enterobacterales (ESBL-PE) are associated with increased mortality rates, prolonged hospital stays and increased costs [4]. Most clinical factors associated with colonization and infection with ESBL-producing organisms involve healthcare exposure, such as hospitalization, residence in a long-term care facility, hemodialysis use and presence of an intravascular catheter [5][6]. Risk factors for community-acquired infections include recent antibiotic therapy, use of corticosteroids, and the presence of a percutaneous feeding tube as well as international travel [7][8]. Carbapenems have been considered the “gold standard” treatment for the treatment of ESBL-PE and have been associated with improved outcomes, even when in vitro activity to other β-lactams is exhibited [9]. These findings cannot be extrapolated to all patients, as a considerable amount of literature has been

published on the use of β-lactams/β-lactamase inhibitor combinations (BLBLI) and specifically piperacillin–tazobactam [10][11][12][13]. In addition, the implementation of carbapenem-sparing strategies has also been applied in ESBL infections in order to combat the overuse of carbapenems and to facilitate antibiotic stewardship programs [14][15][16][17].

2. Piperacillin–Tazobactam

It is clear that piperacillin–tazobactam (PTZ) among non-carbapenem β-lactams represents the most interesting alternative to carbapenems in the treatment of infections causes by ESBL-PE, as well as for de-escalating carbapenems [18]. Despite the fact that a high percent of ESBL isolates demonstrate in vitro susceptibility to PTZ (current break point according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) ≤8 mg/L, and to Clinical & Laboratory Standards Institute (CLSI) ≤16 mg/L), the significance of PTZ for treating ESBL-PE has remained cloudy. Tazobactam by itself is a potent β-lactamase inhibitor. However, Gram-negative bacteria have the ability to produce concomitantly multiple ESBLs and AmpC β-lactamases, as well as possess other resistance mechanisms such as porin mutations and efflux activation, diminishing the activity of PTZ. On the other hand, tazobactam is influenced by the “inoculum effect” [18].

The clinical studies comparing the efficacy of PTZ versus carbapenems in infections caused by ESBL-PE are depicted in **Table 1** [10][11][12][13][19][20][21][22][23][24][25][26][27][28][29][30]. Most comparative studies of PTZ versus carbapenems are retrospective and difficult to be evaluated because of several disagreements [11][12][13][19][20][21][22][24][25][27][28][29][30]. Rodríguez-Baño et al. [10] in 2012 conducted a post hoc analysis of patients with blood stream infection (BSI) due to ESBL-PE derived from 6 published prospective cohorts in Spain. Patients treated either with an active in vitro BLBLI (i.e., amoxicillin-clavulanic acid (AMC) and PTZ) or a carbapenem were compared in 2 cohorts: the empirical therapy cohort (ETC) with 103 patients (AMC 37, PTZ 35, carbapenem 31) and the definitive therapy cohort (DTC) with 174 patients (AMC 36, PTZ 18, carbapenem 120). *E. coli* was isolated in 100%, the source of bacteremia being in 70% urinary or biliary. In 13%, ICU admission at infection onset was necessary, pointing out that most patients were not critically ill. At day 30, mortality rates in the ETC were 9.7% vs. 19.4% and in the DTC 9.3% vs. 16.7% for those given BLBLI and carbapenems respectively (pNS). No association between BLBLI empirical therapy or definitive therapy and increased mortality was observed [10]. Despite the equal clinical validity between the administered antibiotics, the following points seem to compromise the results: (a) only *E. coli* infections were treated, whereas no *K. pneumoniae* isolates with bla_{SHV} production, mostly resistant to tazobactam inhibition by definition, were included; (b) “low inoculum” infections (urinary and biliary tract) were mostly treated. It should be pointed out that when the MIC to PTZ was ≤4 mg/L mortality was 4.5%, mounting to 23% in the case of MIC ≥8 mg/L. Based on their results, Rodríguez-Baño et al. [10] suggested that PTZ should be given with safety only in “low inoculum” infections and whenever the MIC is ≤4 mg/L at a dosage schedule of 4.5 g every 6 h.

Table 1. Clinical studies comparing the efficacy of piperacillin–tazobactam versus carbapenems in infections caused by ESBL-producing Enterobacterales [10][11][12][13][19][20][21][22][23][24][25][26][27][28][29][30].

Study	Country of Study (Period of Study)	Study Design	PTZ (*n*, Number of Participants)	Carbapenems (*n*, Number of Participants)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (PTZ vs Carbapenems)	Comments
Rodríguez-Baño et al. [a] [10]	Spain (2001–2006)	Post hoc analysis of 6 prospective cohorts	Empiric: *n* = 35 Definitive: *n* = 18	Empiric: *n* = 31 Definitive: *n* = 120	*Escherichia coli* (100%)	BSI (100%) -urinary or biliary (70%)	ICU: 13% Severe sepsis or shock: 23%	**30-day mortality** (empiric): 10% vs 19% (ns) **30-day mortality** (definitive): 9% vs 17% (ns)	No association between either empirical or definitive therapy with PTZ and increased mortality
Kang et al. [19]	Korea (2008–2010)	Retrospective	*n* = 36	*n* = 78	*E. coli* (68%) *Klebsiella pneumoniae* (32%)	BSI (100%)	NR	**30-day mortality**: 22% vs 27% (ns)	No difference between PTZ and carbapenem treatment
Tamma et al. [20]	USA (2007–2014)	Retrospective	*n* = 103	*n* = 110	*K. pneumoniae* (68%) *E. coli* (31%) *Proteus mirabilis* (1%)	BSI (100%) -CRBSI (46%) -UTI (21%) -cIAI (17%) -Biliary (9%) - pneumonia (9%)	ICU:34% Neutropenia: 15%	**14-day mortality**: 17% vs 8% ($p < 0.05$) **30-day mortality**: 26% vs 11% ($p < 0.01$)	PTZ inferior to carbapenems for the treatment of ESBL bacteremia. Risk of death 1.92 times higher for patients on empiric PTZ therapy
Ofer-Friedman et al. [11]	Multicenter (USA, Israel) (2008–2012)	Retrospective	*n* = 10	*n* = 69	*E. coli* (53%) *K. pneumoniae* (28%) *P. mirabilis* (19%)	BSI (100%) - pneumonia (34%) -SSTI (28%) -Biliary (17%) -cIAI (9%)	Rapid fatal condition per McCabe score: 39%	**30-day mortality**: 60% vs 34% ($p = 0.10$) **90-day mortality**: 80% vs 48% ($p = 0.05$)	Therapy with PTZ was associated with increased 90-day mortality (adjusted OR, 7.9. $p = 0.03$)
Harris et al. [12]	Singapore (2012–2013)	Retrospective	*n* = 24	*n* = 23	*E. coli* (86%) *K. pneumoniae* (14%)	BSI (100%) -UTI (47%) -Biliary (9%)	ICU: 15%	**30-day mortality**: 8% vs 17% (ns)	No difference between PTZ and carbapenem treatment

Study	Country of Study (Period of Study)	Study Design	PTZ (*n*, Number of Participants)	Carbapenems (*n*, Number of Participants)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (PTZ vs Carbapenems)	Comments
Gutiérrez-Gutiérrez et al. [a] [13]	INCREMENT international project (2004–2013)	Retrospective	Empiric: *n* = 123 Definitive: *n* = 60	Empiric: *n* = 195 Definitive: *n* = 509	*E. coli* (73%) *K. pneumoniae* (19%)	BSI (100%) -UTI (45%) -Biliary (12%)	ICU: 11% Severe sepsis or shock: 32%	**30-day mortality** (empiric): 18% vs 20% (ns) **30-day mortality** (definitive): 10% vs 14% (ns)	No association between either empirical or definitive therapy with PTZ and increased mortality
Ng et al. [21]	Singapore (2011–2013)	Retrospective	*n* = 94	*n* = 57	*E. coli* (67%) *K. pneumoniae* (33%)	BSI (100%) -UTI (59%) -Biliary (9%) - Pneumonia (9%) -cIAI (5%) -CRBSI (4%)	ICU: 9%	**30-day mortality**: 31% vs 30% (ns)	No difference between PTZ and carbapenem treatment
Gudiol et al.[a] [22]	Multicenter (2006–2015)	Retrospective	Empiric: *n* = 44 Definitive: *n* = 12	Empiric: *n* = 126 Definitive: *n* = 234	*E. coli* (74%) *K. pneumoniae* (23%) *K. oxytoca* (1.5%) *Enterobacter cloacae* (1.5%)	BSI (100%) -Primary (53%) -CRBSI (18%) -cIAI (15%) -UTI (7%)	ICU: 18% Septic shock: 22% Hematological neutropenic patients: 100%	**30-day mortality** (empiric): 21% vs 13% (ns) **30-day mortality** (definitive): 6% vs 16% (ns)	PTZ appeared to have similar efficacy to carbapenems in hematological neutropenic patients
Seo et al. [23]	Korea (2013–2015)	Randomized trial	*n* = 33	*n* = 33	*E. coli* (100%)	UTI (100%) BSI (11%)	Septic shock: 30%	**28-day mortality**: 6.1% vs 6.1% (ns)	PTZ appeared to have similar efficacy to ertapenem in UTIs
Yoon et al. [24]	Korea (2011–2013)	Retrospective	*n* = 68	*n* = 82	*E. coli* (100%)	UTI (100%) BSI (15%)	ICU: 25% Septic shock: 16%	**In-hospital mortality**: 4.4% vs 13% (ns)	PTZ appeared to have similar efficacy to ertapenem in UTIs

In the effort to evaluate the efficacy of BLBLI versus carbapenems in patients with a non-urinary source of ESBL-PE bacteremia, Ofer-Friedman et al. [11] performed a multicenter, multinational efficacy analysis from 2008 to 2012 comparing outcomes in patients given a carbapenem (69) versus those treated with PTZ (10). Despite the fact that PTZ was numerically connected with increased 30-day mortality (60% vs. 34%), results were not statistically significant ($p = 0.1$) probably because of the small sample size. However, in terms of 90-day mortality, therapy with

Study	Country of Study (Period of Study)	Study Design	PTZ (*n*, Number of Participants)	Carbapenems (*n*, Number of Participants)	Organism(s)	Site of Infection	Severity of Illness at Infection Onset	Outcome (PTZ vs Carbapenems)	Comments
Ko et al. [a] [25]	Korea (2010–2014)	Retrospective	*n* = 41	*n* = 183	*E. coli* (66%) *K. pneumoniae* (34%)	BSI (100%) -Primary (24%) -CRBSI (3%) -UTI (37%) -cIAI (28%)	ICU: 33%	**30-day mortality**: 6.3% vs 11.4% (ns)	No difference between PTZ and carbapenem treatment
Harris et al. [26]	International, multicenter (2014–2017)	Randomized trial	*n* = 188	*n* = 191	*E. coli* (87%) *K. pneumoniae* (13%)	BSI (100%) - UTI (61%) -cIAI (16%) -CRBSI (2%) - Pneumonia (3%) -Mucositis (5%) -SSTI (1%)	ICU: 7% Neutropenia: 7%	**30-day mortality**: 12.3% vs 3.7% (p = 0.90)	Definitive treatment with PTZ compared with meropenem did not result in a non-inferior 30-day mortality
Benanti et al. [27]	USA (2008–2015)	Retrospective	*n* = 21	*n* = 42	*E. coli* (100%)	BSI (100%) - cIAI (40%) -UTI (10%) -CRBSI (11%) - Pneumonia (11%) -SSTI (10%)	ICU: 30% Neutropenia: 89%	**14-day mortality**: 0% vs 19% (p = 0.04)	Empiric treatment with PTZ not associated with increased mortality in patients with hematologic malignancy
John et al. [28]	USA (2014–2017)	Retrospective	*n* = 66	*n* = 51	*E. coli* (86%) *K. pneumoniae* (14%)	BSI (100%) -UTI (73%) -cIAI (19%) - Pneumonia (1%)	ICU: 38% Septic shock:17%	**In-hospital mortality**: 3% vs 7.8% (ns)	PTZ appeared to have similar efficacy to carbapenems
Nasir et al. [a] [29]	Pakistan (2015–2017)	Retrospective	*n* = 89	*n* = 174	*E. coli* (100%)	BSI (100%) -UTI (66%) -cIAI (23%)	ICU: 38% Septic shock:17%	**In-hospital mortality**: 13% vs 21% (ns)	PTZ appeared to have similar

One year later, Gutiérrez-Gutiérrez et al. [13] published an international observational study (called INCREMENT study), investigating the possibility of replacing carbapenems with BLBLI for treating BSI due to ESBL-PE. The main outcomes were clinical response, as cure/improvement at day 14 and 30-day mortality. Two groups of patients were included—(a) 365 in an empirical therapy cohort (PTZ in 123 cases and a carbapenem in 195) and (b) 601 in a targeted therapy cohort (PTZ in 60 and a carbapenem in 509)—therefore comprising, to date, the largest study cohort. The 14-day cure/improvement rates were, in the first cohort, 78.9% for carbapenems and 80% for BLBLIs (p = 0.81), with mortality rates of 20% vs. 17.6% (p = 0.3), and in the second cohort 90.2% and 85.5% (p = 0.22) with mortality rates of 9.8% vs. 13.9% (p = 0.28) respectively. The authors concluded that “active in vitro BLBLIs are not inferior to carbapenems for the treatment of BSI due to ESBL-PE in different clinical scenarios”, suggesting that BLBLIs may be useful alternatives to carbapenems if used in appropriate doses [13]. An important issue raising doubts of PTZ efficacy is the diminished activity of tazobactam in the presence of a high burden of bacteria with MICs frequently near the breakpoints, whereas the MICs of carbapenems (except ertapenem) are usually several dilutions below the breakpoints rendering, at least from the pharmacokinetic/pharmacodynamic (PK/PD) aspect, the carbapenems advantageous [31]. On the other hand, the type of pathogens seemed to be influential in mortality rates, since *K. pneumoniae* was independently associated with higher death rate than *E.*

Study	Country of Study (Period of Study)	Study Design	PTZ (*n*, Number of Participants)	Carbapenems (*n*, Number of Participants)	Organism(s) [13]	Site of Infection	Severity of Illness at Infection Onset	Outcome (PTZ vs Carbapenems)	Comments
						-CRBSI (3%)			efficacy to carbapenems
Sharara et al. [30]	USA (2014–2016)	Retrospective	*n* = 45	*n* = 141	*E. coli* (56%) *K. pneumoniae* (30%) *P. mirabilis* (10%) *K. oxytoca* (4%)	UTI (100%)	ICU: 26%	**30-day mortality**: 4% vs 7% (ns)	PTZ appeared to have similar efficacy to carbapenems. Patients treated with carbapenem had higher incident of carbapenem-resistant organism isolated in 60 d (p = 0.09)

a dose of 3.375 g/8 h with 4 h infusion. Therefore, the mode of administration is important to evaluate when considering the efficacy of PTZ in the comparable arms of therapy [21].

In a prospective randomized open-label comparison trial with a limited number of 64 patients with febrile healthcare-associated complicated urinary tract infections (cUTIs) with ESBL-producing *E. coli*, the efficacy of PTZ was compared to ertapenem [23]. Regarding clinical and microbiological success of PTZ versus ertapenem, the former reached 93.9% vs. 97.0% and 97.0% vs. 97.0% respectively, with a 28-day mortality of 6.1% equal in the two groups. The authors concluded that "PTZ is effective in the treatment of UTIs caused by ESBL-producing *E. coli* whenever the MIC is ≤1 mg/L".

BSI, blood stream infection; CRBSI, catheter-related blood stream infection; cIAI, complicated intra-abdominal infection; ESBL, extended spectrum β-lactamases; ICU, intensive care unit; NR, not reported; ns, not significant; OR, odds ratio; PTZ, piperacillin-tazobactam; SSTI, skin and tissue infections; UTI, urinary tract infection; vs, versus. [a] Studies including ESBL-PE (possessing MIC to PTZ of ≤8μg/mL) was performed [24]. No significant difference between PTZ and ertapenem regarding the primary end-points of the study, that is, microbiological eradication failure (4.4% vs. 4.9%), in-hospital mortality (4.4% vs. 13.4%) and change of initial antibiotic regimen (14.7% vs. 22.0%), were observed. In the multivariate analysis, predictors of treatment failure included septic shock and recent administration of immunosuppressive agents; however, the type of the administered antibiotic was not associated with treatment outcome.

Similarly, a retrospective observational targeted study of PTZ (68 patients) vs. ertapenem (82 patients) for acute pyelonephritis caused by ESBL-PE (possessing MIC to β-lactamase inhibitors versus

The results of two metanalyses referring to carbapenems versus alternative antibiotics for treating ESBL-PE BSI, both published in 2018, are quite interesting [32][33]. In the first metanalysis, 35 publications (until 2016) fulfilled the inclusion criteria [32]. Whenever antibiotics were given empirically, no significant differences related to overall mortality were observed between carbapenems and non-carbapenems. As it concerns definitive therapy, overall mortality was lower for patients given carbapenems compared to cephalosporins and non-BLBLIs, whereas no differences between carbapenems and BLBLIs, as well as quinolones and aminoglycosides, were observed. Despite the absence of differences when BLBLIs were compared to carbapenems, the authors pointed out the lack of robust data derived from randomized controlled trials, as well as the heterogeneity of the study population.

In the second metanalysis, 25 observational studies (until 2017) including 3847 patients were analyzed [33]. Thirty-day mortality of BLBLIs or PTZ was not statistically different from carbapenems either as empirical or definitive therapy. Moreover, the authors suggested that PTZ may be considered as an alternative treatment for ESBL-PE

BSI, particularly when the MIC is low (≤4 mg/L) and/or the source of the infection is abdominal or genito-urinary. Sfeir et al. [33] also pointed out the limitations encountered in their review, such as the observational character and the heterogeneity of the studied population, as well as the lack of information on the mode of administration of PTZ (i.e., high dose and continuous 4 h infusion for achieving adequate PK/PDs therapeutic targets [10]). However, the reported limitations should not be an obstacle for suggesting PTZ at high dose and continuous infusion as a non-inferior carbapenem-sparing agent against ESBL-PE. It is of great importance to mention that PTZ is not suitable for deep-seated infections associated with high inoculum (where carbapenems should be preferred), since PTZ possesses a strong inoculum effect leading to ≥8-fold increase in the MIC [34].

The results regarding the efficacy of PTZ in infections caused by ESBL-PE are based mainly on retrospective studies and are controversial (**Table 1**). The so-called MERINO trial [26][35] was conducted to answer the key question “Can PTZ be used as carbapenem sparing therapy in patients with bloodstream infections caused by ceftriaxone-resistant *E. coli* or *K. pneumoniae* that test susceptible to PTZ and meropenem?”. The MERINO study was an international, multicenter, noninferiority, open-label, parallel group, randomized clinical trial comparing 30-day mortality of PTZ (4.5 g q6h) vs. meropenem (1 h q8h) both infused over 30 min, as definitive therapy in adult patients with ceftriaxone-resistant *E. coli* or *K. pneumoniae* BSI. Randomization was performed within 72 h of blood culture collection, and patients received study drugs for a minimum of 4 d and a maximum of 14 d after randomization with an arbitrary length of treatment arranged by the treating physician. A 5% noninferiority margin was used. Patients were screened for enrollment in 26 hospitals in 9 countries (Australia, New Zealand, Singapore, Italy, Turkey, Lebanon, South Africa, South Arabia and Canada) starting February 2014 until July 2017. Stratification included infecting species, presumed source of infection (UTI or elsewhere) and infection severity (Pitt bacteremia score ≤4 or >4). Primary outcome was all-cause mortality at 30 d post randomization, with secondary outcomes including (a) time to clinical and microbiological resolution of infection; (b) clinical and microbiological success at day 4 post randomization; (c) microbiologic resolution of infection; (d) bloodstream infection relapse; (e) superinfection with meropenem or PTZ-resistant microorganisms or *Clostridium difficile* infections. Finally, out of 1646 screened patients, 378 were randomized (191 in meropenem and 188 in PTZ group). Although balanced with respect to baseline characteristics, more patients in the meropenem group had diabetes, a urinary source of bacteremia and higher APACHE II scores (41.4% vs. 31.4%, 67.0% vs. 54.8% and 21.0% vs. 17.9% respectively), whereas in the PTZ group more patients were immunocompromised (27.1% vs. 20.9% accordingly). A total of 23 patients (12.3%) receiving PTZ vs. 7 (3.7%) in the meropenem group met the primary outcome of 30-day mortality (p = 0.90 for noninferiority). In microbiological analysis, a total of 306 isolates were available (266 *E. coli* and 40 *K. pneumoniae*) with median MIC to PTZ of 2 mg/L (IQR 1.5–4 mg/L) and median MIC to meropenem of 0.023 mg/L (IQR 0.016–0.032 mg/L). ESBL genes were confirmed in 85.3% isolates with 10.2% possessing acquired AmpC genes and 2% both. Narrow-spectrum oxacillinases (bla_{OXA-1}), which may compromise β-lactamase inhibition by tazobactam, were identified in 67.6% of the strains. The authors stated that “PTZ should no longer be considered an alternative to meropenem for definitive treatment of bloodstream infections due to ceftriaxone-resistant *E. coli* and *K. pneumoniae*” [26]. However, certain limitations should be taken into consideration: (a) the inherent delay in blood cultures processing and susceptibility results, indicating that empiric therapy was not throughout under control; (b) the fact that “step down therapy” occurred only in 20.1% of carbapenem-treated patients; (c) crossover

of patients from one group to the other was allowed; (d) the lack of information regarding adequate source control; (e) the presence of acquired AmpC in 10.2% of the strains could have an impact on PTZ efficacy, since such enzymes reduce β-lactamase inhibition by tazobactam at least in vitro [9]; (f) due to unblind study design, investigators were aware of the treatment allocation, prompting therefore early cessation of PTZ; (g) the acuity of infection was lower than expected; (h) the high percentage of patients (40.7%) with resolved signs of infection at the randomization day, providing strong evidence against the noninferiority of PTZ [26][35].

Finally, certain questions were left unanswered in the MERINO trial [26]. Questions that need to be answered, however, are whether PTZ given in extended or constant infusion is efficacious, as well as the effectiveness of PTZ in cases of empirical therapy of bacteremia or in the treatment of non-bacteremic ESBL-PE infections. Probably, a European plus a USA blinded trial (similar to MERINO), taking into account the reported limitations analyzed, could give answers to the existing questions. In the meantime, it seems preferable, whenever a carbapenem-sparing decision is pending, to seriously consider the Tamma and Rodríguez-Baño et al. [18] positions.

3. Ceftolozane–Tazobactam

Ceftolozane–tazobactam is a novel combination of a cephalosporin with a β-lactamase inhibitor that exhibits excellent in vitro activity against a broad spectrum of Enterobacterales and *Pseudomonas aeruginosa*, including ESBL strains, and has been recently approved for the treatment of complicated intra-abdominal infections (cIAI) and cUTI [36]. The in vitro activity of ceftolozane–tazobactam against ESBL-PE from U.S. hospitals revealed an overall susceptibility of 83.9% (CLSI/EUCAST breakpoints) to ceftolozane–tazobactam. Ceftolozane–tazobactam inhibited 95.5% of the *E. coli* isolates, but only 83% of *K. pneumoniae* producing ESBL. Regarding ESBL-encoding genes, ceftolozane–tazobactam inhibited 92.9% of the isolates harboring bla_{CTX-M} and exhibited limited activity against isolates carrying bla_{SHV} (61.1% susceptible) [37]. In phase III randomized clinical trials, ceftolozane–tazobactam (in combination with metronidazole) demonstrated similar efficacy to meropenem for the treatment of cIAIs [38] and superior efficacy to levofloxacin for the treatment of cUTIs, including pyelonephritis [39]. Also, in a phase 3 trial with nosocomial infections, ceftolozane–tazobactam was compared to meropenem and in patients with ESBL-PE, and clinical cure rates were 57.1% (48/84) and 61.6% (45/73) respectively [40]. In a pooled analysis of phase III clinical trials, a total of 159 ESBL-PE isolates from the microbiologically evaluable population, mostly *E. coli* (68.6%), were identified. Overall, 72.3% of ESBL isolates were susceptible to ceftolozane–tazobactam versus 98.3% to meropenem, whereas only 24.1% were susceptible to levofloxacin at EUCAST breakpoints. Clinical cure rates against ESBL isolates in cUTIs treated with ceftolozane–tazobactam and levofloxacin were 95.8% and 82.6% respectively, whereas in cIAIs, clinical cure rates depicted were 98.1% for the ceftolozane–tazobactam group and 88.5% for the meropenem group [41]. It is of great significance to point out that, in a cost effectiveness analysis comparing carbapenem-sparing agents versus meropenem, patients with cUTIs due to ESBL receiving ceftolozane–tazobactam were found cost-effective compared to meropenem [42]. Although the limited data available for ESBL pathogens are extrapolated from clinical trials to preclude robust analysis, ceftolozane–tazobactam seems as an attractive option for a carbapenem-sparing strategy depending on local antibiotic

stewardship decisions. However, more evidence is needed to confirm the exact place of ceftolozane–tazobactam for ESBL infections.

4. Ceftazidime–Avibactam

Avibactam, a novel non-b-lactam, b-lactamase inhibitor, restores the activity of ceftazidime against the majority of β-lactamases (ESBLs and carbapenemases, including *Klebsiella pneumoniae* carbapenemase (KPCs) and OXA-48), resulting in activity of ceftazidime–avibactam combination against a wide range of MDR Gram-negative bacteria [43][44]. In vitro activity of ceftazidime–avibactam against Enterobacterales from 18 European countries as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program from 2012 to 2015 revealed ceftazidime–avibactam was the most active agent, compared with all other tested comparator agents, against non-susceptible ceftazidime isolates (97.7% susceptible) [45]. A post hoc analysis of phase 2 trials summarizing the results of ESBL-PE isolates recovered at baseline revealed a favorable outcome in the ceftazidime–avibactam and meropenem arms in 85.7% and 80.0% of patients, respectively [46]. Similarly, clinical cure rates from patients enrolled in phase 3 clinical trial regarding cUTIs revealed efficacies of 90.3% and 89.1% for the ceftazidime–avibactam and doripenem groups accordingly [47], highlighting a potential role for ESBL infections. However, it should be taken into consideration that ceftazidime–avibactam is one of the limited options for carbapenemase-producing Enterobacterales [44]. Therefore, it should be preserved for the treatment of KPC and OXA-48 producers and should not be recommended as a carbapenem-sparing strategy.

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